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⑰ **Camptothecin derivatives, processes for preparing same, formulations containing such derivatives and their use.**

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JOURNAL OF THE CHEMICAL SOCIETY, Perkin Transactions 1, vol. 5, 1981, pages 1563-8, London (GB); T. KAMETANI et al.: "Studies on the syntheses of heterocyclic compounds. Part 878, 1. Synthesis of (plus/minus)-Camptothecin and (plus/minus)-10-Methoxycamptothecin via Enamine Annulation"

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## Description

This invention relates to new 10-substituted camptothecin derivatives possessing anti-tumor activity (including carcinostatic activity) and to processes for the preparation of such derivatives. More particularly, this invention relates to new 5-R<sup>1</sup>-7-R<sup>2</sup>-camptothecin derivatives carrying a substituent R<sup>3</sup> in the 10-position thereof and possessing anti-tumor activity, good absorbability, and a low level of toxicity, as well as to processes for the preparation of 10-substituted camptothecin derivatives.

Camptothecin is a cytotoxic alkaloid isolated from leaves and barks of *Camptotheca acuminata* (Nyssaceae), a plant native to China, which has a pentacyclic structure consisting of a characteristic fused 5-ring system of quinoline (rings A and B), pyrroline (ring C),  $\alpha$ -pyridone (ring D) and a six-membered lactone (ring E) and is distinguished by displaying a strong inhibitory activity toward biosynthesis of nucleic acids. In addition, camptothecin is a unique anti-tumor substance characterized by its rapid and reversible action and its lack of any cross-tolerance with the existing anti-tumor agents and by exhibiting a strong anti-tumor activity against experimentally transplanted carcinoma such as leukemia L-1210 in mice or Walker 256 tumor in rats. Although camptothecin is still regarded as one of the most potent substances possessing anti-tumor activity, the use of this compound itself for clinical treatments is significantly limited because of high toxicity.

Accordingly, a number of attempts have been made to reduce toxicity of camptothecin while maintaining its anti-tumor activity by converting camptothecin chemically into its derivatives. The chemical modifications so far reported are mainly about the rings D and/or E of camptothecin, but the results of such modifications revealed only failure in maintaining expected anti-tumor activity and poor improvement in toxicity [J. Med. Chem., 19 (1976), 675]. From the chemotherapeutic point of view, therefore, it is of importance that the chemical modifications of camptothecin should be restricted in the rings A, B and C without effecting any change in the rings D and E which are conceivably one of the essential structural elements for the expression of the above mentioned characteristic biological activities.

J. Chem. Soc. Perkin Transactions 1, vol. 5, 1981, pages 1563-8, London, T. Kametani et al., discloses a process for the total synthesis of camptothecin and 10-methoxycamptothecin from 3,4-dihydro-1-methyl- $\beta$ -carboline. The products are racemic.

Except for a method for functionalizing the 12-position of camptothecin reported in 1976 which comprises a series of troublesome conversion and purification operations starting with nitration at 12-position [P. Pei-chuang et al., Hau Hsueh Hsueh Pao, Vol. 33 (1975) 71; Chem. Abstr. 84 (1976) 115629p], however, no success was reported until 1979 in connection with chemical functionalization of camptothecin in a moiety involving the rings A, B and C. This is probably attributable to the reason that camptothecin itself is only sparingly soluble in various organic solvents and that camptothecin possessing the nature of heterocyclic rings in its molecule is resistant to the so-called electrophilic reactions conventionally carried out on aromatic rings. In the present status, such obstacles strongly refuse chemical modifications of camptothecin contemplated on the desk for preparing new classes for derivatives thereof.

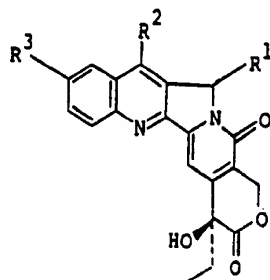
Under the above mentioned circumstances, the present inventors previously found together with co-workers processes for introducing (1) hydroxymethyl group into 7-position, (2) hydroxy group into 5-position and (3) an alkyl or aralkyl group into 7-position of camptothecin efficiently in a single step, and prepared a great number of new camptothecin derivatives possessing anti-tumor activity with slight toxicity from 5- and/or 7-substituted camptothecin obtained according to the above processes, by chemical modification of the 5- and/or 7-substituent (U.S. Patents 4,399,276 and 4,399,282). However, the sorts of camptothecin derivatives prepared according to these processes are still limitative.

Noteworthy in recent years is that 10-hydroxycamptothecin isolated from *Camptotheca acuminata* was reported to be lower in toxicity than camptothecin itself but higher in anti-tumor activity (a certain medical magazine in China, 1978). For further extensive researches on the relation between substituents in camptothecin derivatives and anti-tumor activity and/or toxicity, therefore, there is still a great demand in this art for developing further new classes of camptothecin derivatives possessing a low level of toxicity while maintaining the inherent anti-tumor activity by chemical modifications of camptothecin itself or derivatives thereof in a simple manner.

The present invention is based upon extensive research into chemically modifying the 10-position of camptothecin or 5- and/or 7-substituted derivatives thereof without destruction of the structure of rings D and E. As a result of such research it has been found surprisingly that an alkoxy group, an acyloxy group or hydroxyl group can be introduced into 10-position of camptothecin or a 5- and/or 7-substituted derivative thereof by treating camptothecin or a 5- and/or 7-substituted derivative thereof with a peroxidant and then reacting the resultant N-oxide compound with an active hydrogen compound in the presence of an acid under irradiation with UV-rays. In addition, extensive research has developed a method for introducing a hydroxy group, a nitrogen-containing substituent (such as a nitro group or an amino group) or a halogen atom into the 10-position of camptothecin. Thus, it has been found surprisingly that a nitro group can be introduced into the 10-position of camptothecin by catalytically hydrogenating camptothecin in a liquid vehicle such as acetic acid or dioxaneacetic acid in the presence of a noble metal catalyst, such as platinum oxide catalyst, treating the resultant 1,2,6,7-tetrahydrocamptothecin with an acylating agent, and then treating the thus obtained 1-acyl-1,2,6,7-tetrahydrocamptothecin with Conc. nitric acid in the presence of sulfuric acid, and that the nitro group in the 10-position of the resultant 1-acyl-10-nitro-1,2,6,7-tetrahydro-

camptothecin can be converted, preferably after removing the acyl group by hydrolysis and oxidation to cause dehydrogenation of the saturated ring, into a free amino group by reduction, and the amino group can further be converted according to a variety of methods known per se into an alkylamino group by alkylation, into an acylamino group by acylation or into a hydroxy group or a halogen substituent by diazotization followed by hydrolysis or a Sandmeyer reaction.

In accordance with the present invention, there are provided new 10-substituted camptothecin derivatives of the general formula:



(I)

wherein R<sup>1</sup> is a hydrogen atom, a C<sub>1</sub>—C<sub>30</sub> alkyl group, a C<sub>5</sub>—C<sub>8</sub> cycloalkyl group, a hydroxyl group, a C<sub>1</sub>—C<sub>30</sub> alkoxy group or a C<sub>1</sub>—C<sub>17</sub> acyloxy group, R<sup>2</sup> is a C<sub>1</sub>—C<sub>30</sub> alkyl group, a C<sub>5</sub>—C<sub>8</sub> cycloalkyl group, a phenylalkyl group, a naphthylalkyl group, a hydroxymethyl group, a carboxymethyl group or a C<sub>1</sub>—C<sub>17</sub> acyloxymethyl group, and R<sup>3</sup> is the grouping —XR' (in which R' is a hydrogen atom, a C<sub>1</sub>—C<sub>30</sub> alkyl group, a C<sub>5</sub>—C<sub>8</sub> cycloalkyl group or a C<sub>1</sub>—C<sub>17</sub> acyl group and X is an oxygen atom or a sulfur atom), and wherein the alkyl, alkoxy, acyl and acyloxy groups may be substituted with one or more halo, nitro, amino, carboalkoxy, alkylamino, dialkylamino or alkoxy groups as defined above.

In the above general formula (I), R<sup>1</sup> is preferably a hydrogen atom. When R<sup>1</sup>, R<sup>2</sup> or R' stands for an alkyl group, it has 1—30 carbon atoms but in view of the availability of alkylating reactants, the alkyl group preferably has 1—18 carbon atoms. Illustrative of the alkyl group are, for example, straight or branched chain alkyl groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentyl, isopentyl, n-hexyl, n-heptyl, n-octyl, 2-ethylhexyl, n-nonyl, n-decyl, undecyl, dodecyl, myristyl, heptadecyl, octadecyl and eicosyl groups. R<sup>1</sup>, R<sup>2</sup> or R' may be a C<sub>5</sub>—C<sub>8</sub> cycloalkyl group. When R<sup>1</sup> stands for an alkoxy group, the alkyl moiety thereof is as defined above. Preferable examples of the alkoxy group are those derived from straight or branched chain lower alkyl groups with 1—8 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentyloxy, isopentyloxy, n-hexyloxy, n-heptyloxy, n-octyloxy and 2-ethylhexyloxy groups. When R<sup>1</sup> stands for an acyloxy group, the alkyl moiety thereof is a straight or branched chain alkyl group with 1—17 carbon atoms, such as acetoxyl, propionyl, n-butyryl, isobutyryl, valeryl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl and octadecanoyl groups. The term "acyloxy group" includes the formyl group as well. The acyl moiety of the acyloxy group may be derived from aromatic carboxylic acids, heterocyclic carboxylic acids, aralkylcarboxylic acids and alkyl and aromatic sulfonic acids. These acids may contain one or more unsaturated bonds in the molecule and carry one or more halogen atoms, amino groups or hydroxyl groups. Illustrative of these acids other than the aliphatic carboxylic acids mentioned in the above acyloxy groups are, for example, benzoic acid, halo-, amino- or hydroxy-substituted benzoic acids, nicotinic acid, phenylacetic acid, ethanesulfonic acid or benzenesulfonic acids, various kinds of amino acids and halogen-substituted aliphatic acids such as monochloroacetic acid. When R<sup>2</sup> stands for a phenylalkyl or naphthylalkyl group, its preferable examples include benzyl, phenethyl, phenylpropyl and 1- or 2-naphthylmethyl groups. When R<sup>2</sup> stands for an acyloxymethyl group, the acyl moiety is as defined above. Preferable examples of the acyloxymethyl group include those having an acyl moiety with 1—8 carbon atoms, such as acetoxymethyl, ethanesulfonyloxymethyl, propionylloxymethyl, butyryloxymethyl, hexanoyloxymethyl, heptanoyloxymethyl, p-toluenesulfonyloxymethyl, benzoyloxymethyl, phenylacetoxymethyl, nicotinoyloxymethyl and monochloroacetoxymethyl groups. When R<sup>1</sup> stands for an acyl group, the acyl group is as defined above with respect to the case of R<sup>1</sup> being an acyloxy group. When R<sup>2</sup> stands for an alkylamino group, the alkyl moiety is a lower alkyl group with 1—8 carbon atoms. Illustrative of the alkylamino group are, for example, methylamino, ethylamino, propylamino, isopropylamino, n-butylamino, tert-butylamino, pentylamino, hexylamino, heptylamino and octylamino groups. When R<sup>3</sup> stands for an acylamino group, the acyl moiety is as defined above with respect to the case of R<sup>1</sup> being an acyloxy group. Preferable examples of halogen atoms include chlorine and bromine atoms.

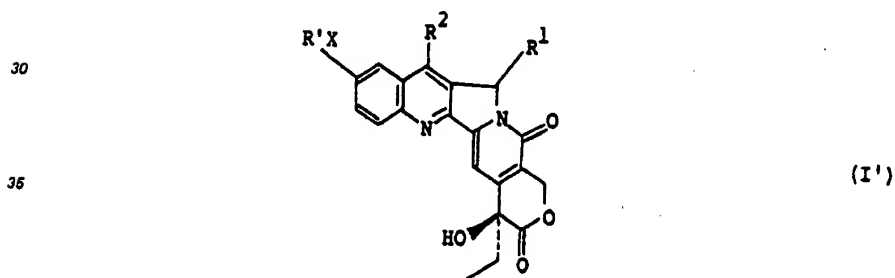
The above mentioned alkyl and alkoxy groups may contain, as in the case of acyl or acyloxy groups, one or more substituent halo (especially chloro), nitro, amino, carboalkoxy, alkylamino, dialkylamino or alkoxy groups as defined above.

The new 10-substituted camptothecin derivatives of the present invention represented by the general formula (I) possess anti-tumor activity with reduced toxicity.

Preferred classes and compounds of the invention are 10 - hydroxy - 7 -  $C_{1-30}$  - alkylcamptothecin, 10 - hydroxy - 7 - phenylalkylcamptothecin, 10 - hydroxy - 7 - naphthylalkylcamptothecin, 10 - hydroxy - 7 - hydroxymethylcamptothecin, 10 - hydroxy - 7 -  $C_{1-17}$  - acyloxymethylcamptothecin, 10 - hydroxy - 7 - carboxymethylcamptothecin, 10 -  $C_{1-30}$  - alkoxy - 7 -  $C_{1-30}$  - alkoxy - 7 -  $C_{1-30}$  - alkylcamptothecin, 10 -  $C_{1-30}$  - alkoxy - 7 - phenylalkylcamptothecin, 10 -  $C_{1-30}$  - alkoxy - 7 - naphthylalkylcamptothecin, 10 -  $C_{1-30}$  - alkoxy - 7 - hydroxymethylcamptothecin, 10 -  $C_{1-30}$  - alkoxy - 7 -  $C_{1-17}$  - acyloxymethylcamptothecin, 10 -  $C_{1-17}$  - acyloxy - 7 -  $C_{1-30}$  - alkylcamptothecin, 10 -  $C_{1-17}$  - acyloxy - 7 - phenylalkyl - or 7 - naphthylalkylcamptothecin, 10 -  $C_{1-17}$  - acyloxy - 7 - hydroxymethylcamptothecin, 10 -  $C_{1-17}$  - acyloxy - 7 -  $C_{1-17}$  - acyloxymethylcamptothecin, the alkyl, alkoxy, acyl and acyloxy groups being optionally substituted as defined above.

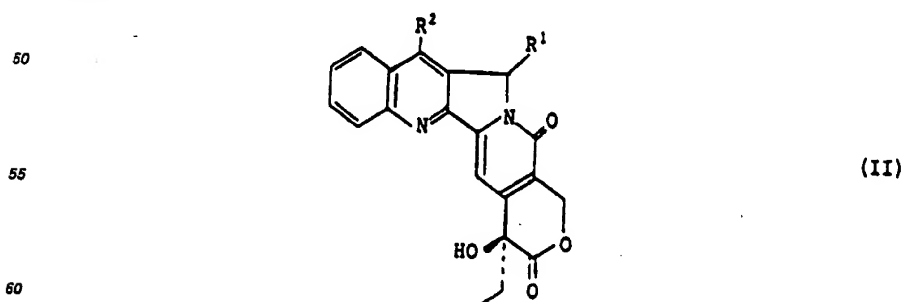
Illustrative of 10-substituted camptothecin derivatives obtained by this invention, as further described below, are 10 - hydroxycamptothecin (10 - hydroxy - CPT; "camptothecin" is hereinafter referred to in the present description simply as ("CPT"), 10 - methoxy - CPT, 10 - ethoxy - CPT, 10 - octyloxy - CPT, 10 - acetoxy - CPT, 10 - propionyloxy - CPT, 10 - hexanoyloxy - CPT, 10 - [(carboethoxymethyl)thio]CPT, 10 - hydroxy - 5 - methyl - CPT, 10 - hydroxy - 5 - ethyl - CPT, 10 - hydroxy - 5 - methoxy - CPT, 10 - hydroxy - 5 - propoxy - CPT, 10 - hydroxy - 5 - acetoxy - CPT, 10 - hydroxy - 7 - hydroxymethyl - CPT, 10 - hydroxy - 7 - methyl - CPT, 10 - hydroxy - 7 - ethyl - CPT, 10 - hydroxy - 7 - propyl - CPT, 10 - hydroxy - 7 - benzyl - CPT, 10 - hydroxy - 7 - acetoxymethyl - CPT, 10 - methoxy - 5 - ethyl - CPT, 10 - methoxy - 7 - ethyl - CPT, 10 - acetoxy - 7 - benzyl - CPT, 10 - propionyloxy - 7 - octanoyloxy - CPT, 10 - nitro - CPT, 10 - amino - CPT, 10 - methylamino - CPT, 10 - chloro - CPT, 10 - bromo - CPT, 7 - ethyl - 5,10 - dihydroxy - CPT, 7 - ethyl - 10 - hydroxy - 5 - methoxy - CPT and 7 - acetoxy - 10 - hydroxy - 5 - methoxy - CPT.

Thus, the invention also provides a process for the preparation of 10-substituted camptothecin derivatives of the general formula:



40 wherein  $R^1$  is a hydrogen atom, a  $C_1-C_{30}$  alkyl group, a  $C_5-C_8$  cycloalkyl group, a hydroxyl group, a  $C_1-C_{30}$  alkoxy group or a  $C_1-C_{17}$  acyloxy group,  $R^2$  is a hydrogen atom, a  $C_1-C_{30}$  alkyl group, a  $C_5-C_8$  cycloalkyl group, a phenylalkyl group, a naphthylalkyl group, a hydroxymethyl group, a carboxymethyl group or a  $C_1-C_{17}$  acyloxymethyl group,  $R^1$  is a hydrogen atom, a  $C_1-C_{30}$  alkyl group, a  $C_5-C_8$  cycloalkyl group, or a  $C_1-C_{17}$  acyl group, and X is an oxygen group, or a  $C_1-C_{17}$  acyl group, and X is an oxygen atom or a sulfur atom, the alkyl, alkoxy, acyl and acyloxy groups being optionally substituted as defined above,

45 characterized by treating camptothecin or a 5- and/or 7-substituted camptothecin derivative of the general formula:



wherein  $R^1$  and  $R^2$  have the same meanings as given above, with a peroxidant in a liquid vehicle and then reacting the resultant camptothecin-1-oxide or 5- and/or 7-substituted camptothecin-1-oxide derivative with an active hydrogen-containing reagent of the general formula:



wherein R' and X have the same meanings as given above, in the presence of an acid under irradiation with UV-rays.

The 5- and/or 7-substituted camptothecin derivatives of the general formula (II) used as starting materials are known or can be prepared according to the known prior art processes.

5 The intermediate 5- and/or 7-substituted camptothecin-1-oxide derivatives are novel compounds and are included within the present invention. The preparation of the 5- and/or 7-substituted camptothecin-1-oxide derivatives is also included within the present invention.

In the first step, the starting camptothecin or 5- and/or 7-substituted camptothecin derivatives used are reacted in a liquid vehicle with a peroxidant to the corresponding-1-oxides (N-oxides). The peroxidant 10 utilizable in the first step for N-oxidation of the ring B (pyridine ring) is selected from hydrogen peroxide, inorganic and organic peracids and salts thereof. Preferable examples of the peroxidant include hydrogen peroxide, peracetic acid, perbenzoic acid, m-chloroperbenzoic acid and a persulfate. The use of hydrogen peroxide in acetic acid is desirable as a higher yield of the N-oxide product is expected thereby. Illustrative of the liquid vehicle are, for example, glacial acetic acid, an aqueous acetic acid solution, hydrocarbons 15 such as benzene and hexane, chlorinated hydrocarbons such as chloroform and methylene chloride, and ethers such as dioxane.

In an embodiment wherein hydrogen peroxide is used for N-oxidation, the operation itself is carried out in a manner similar to that described, for example, in Mosher et al., *Org. Syn.* 33, 79 (1953) or Ochiai et al., *J. Pharm. Soc. Japan* 71, 1385 (1951); the starting camptothecin derivative of the general formula (II) is 20 suspended or dissolved in acetic acid and treated under agitation with hydrogen peroxide (usually about 30% in strength). The selection of a temperature range from 65°C to 70°C is adequate for this reaction. Although a theoretically needed amount of hydrogen peroxide is one mol per mol of the starting camptothecin derivative, the use of a larger excess (about 30 molar proportion) of hydrogen peroxide is preferable. Under such condition, N-oxidation of the starting camptothecin derivative is completed 25 normally within 4 hours.

In another embodiment wherein a peracid is used for N-oxidation, the operation itself is carried out in a manner similar to that described, for example, in Herz et al., *J. Am. Chem. Soc.* 76, 4184 (1954); the starting camptothecin derivative of the general formula (II) is treated, for example, with peracetic acid (usually 40% 30 in concentration) and sodium acetate or with perbenzoic acid in benzene. It is possible to use m-chloroperbenzoic acid as the peroxidant in chloroform or ethylene chloride. It is also possible to use sodium persulfate under similar conditions.

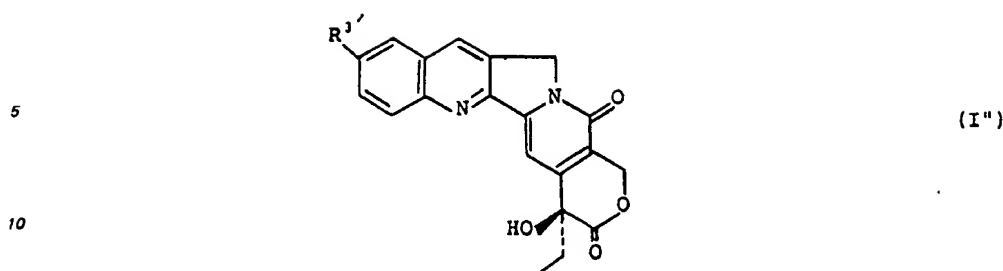
The resultant N-oxide intermediate product can be isolated in a highly pure form by concentrating the reaction mixture under reduced pressure to a volume of about 1/5—1/10, diluting the concentrate with a large excess of ice water, collecting the resultant N-oxide precipitated as needle crystals by filtration, and 35 drying the crystals under subatmospheric pressure.

In the second step, the intermediately formed N-oxide is dissolved in a solvent and treated with an active hydrogen-containing reagent of the general formula (III) in the presence of an acid under irradiation of UV-rays. Preferred as the solvent in this reaction are dioxane, acetonitrile, chloroform, methylene chloride, glyme, diglyme and a mixture of these.

40 Illustrative of the active hydrogen-containing reagent of the general formula (III) are, for example, water, hydrogen sulfide, a monohydric alcohol such as methanol, ethanol, propanol or butanol, an organic acid such as acetic acid or propionic acid, and an alkylmercaptan such as methylmercaptan, ethylmercaptan or mercaptoacetic acid esters. Preferable examples of the acid to be present in the reaction system include mineral acids such as sulfuric acid and perchloric acid, organic sulfonic acids such as 45 ethanesulfonic acid and p-toluenesulfonic acid, Lewis acids such as boron trifluoride-etherate, and organic carboxylic acids such as acetic acid and propionic acid. A good result can be obtained when the acid is used in an amount of 10—15 molar equivalents. The operation for irradiating the reaction mixture with UV-rays is performed according to a known conventional method. The irradiation time is usually between 15—100 minutes and a commercially available high voltage mercury lamp can be used as a source of UV-rays. In 50 case acetic or propionic acid is used as the acid to be present in the reaction system, it also functions as a solvent.

According to the two-step reaction referred to above, the starting camptothecin or a 5- and/or 7-substituted derivative thereof is first converted into the corresponding N-oxide and then the grouping R'X— in the active hydrogen-containing reagent of the general formula (III) is introduced into 10-position of 55 camptothecin or a derivative thereof with simultaneous elimination of the oxygen atom in 1-position under irradiation of UV-rays. The reaction mixture thus treated contains two kinds of product, one being a small amount of 1-deoxygenated product (the starting material) and the other being the end product carrying the substituent —XR' in its 10-position. These products can be separated by HPLC or column chromatography on silica gel and the recovered starting material can be used for the next batch. The end product can be 60 purified, if necessary, by way of chromatography or the so-called recrystallization method.

The invention also provides a process for the preparation of 10-substituted camptothecin derivatives of the general formula;



wherein  $R''$  is a nitro group, an amino group, a  $C_1-C_8$  alkylamino group, a  $C_1-C_{17}$  acylamino group, a hydroxyl group or a halogen atom, the alkyl and acyl groups being optionally substituted as defined above; which process comprises catalytically hydrogenating camptothecin in a solvent under atmospheric pressure in the presence of a noble metal catalyst, treating the resultant 1,2,6,7-tetrahydrocamptothecin with an acylating agent to introduce an acyl group into the 1-position, treating the thus obtained 1-acyl-1,2,6,7-tetrahydrocamptothecin with a mixture of nitric acid and sulfuric acid, eliminating the 1-acyl group in the resultant 1-acyl-10-nitro-1,2,6,7-tetrahydrocamptothecin by hydrolysis and treating the resultant 10-nitro-1,2,6,7-tetrahydrocamptothecin with an oxidizing agent to cause dehydrogenation, and if desired, reducing the resultant 10-nitro-camptothecin or 10-nitro-1,2,6,7-tetrahydrocamptothecin to convert the nitro group into an amino group prior to dehydrogenation, and then modifying the amino group by N-alkylation or N-acylation or by diazotization followed by hydrolysis or a Sandmeyer reaction, and if necessary, treating the resulting compound with an oxidizing agent for dehydrogenation of the saturated ring.

In the first step for hydrogenating the ring B (the pyridine ring), camptothecin is catalytically hydrogenated at room temperature in a solvent such as acetic acid or dioxane-hydrochloric acid under atmospheric pressure by the aid of a noble metal catalyst until the theoretical amount of hydrogen is absorbed. The hydrogenation reaction will be completed usually within 2 hours. Preferable examples of the noble metal hydrogenation catalyst include platinum black, platinum oxide, palladium black, and palladium oxide as such or in the form carried on carbon black. These catalysts are well known in the field of hydrogenation. The reaction mixture is then filtered to remove the catalyst, and the filtrate is concentrated. The residue is then dissolved and subjected to column chromatography on silica gel to purify the hydrogenated product. A small amount of unreacted camptothecin can be recovered by this purification treatment.

In the second step, the resultant 1,2,6,7-tetrahydrocamptothecin is treated with an acylating agent under the conditions known per for acylation. Any of the known conventional acylating agents, for example, acids in reactive functional form can be used for this purpose. Illustrative of the acylating agent are acetic anhydride, acetyl halide or the like lower fatty acid anhydride or halide, benzoyl chloride or the like aromatic acid halide, and p-toluenesulfonyl halides or the like sulfonyl halides. An acid-binding agent for this acylation is preferably a tertiary amine or a weak inorganic base. The use of triethylamine or pyridine is desirable. By this acylation, 1-acylated 1,2,6,7-tetrahydrocamptothecin is obtained in a high yield (above 70%) with a small amount of unreacted starting material. As 1,2,6,7-tetrahydrocamptothecin has hydroxyl group in 20-position thereof, acylation of 20-hydroxyl group also proceeds simultaneously with N-acylation of 1-position. However, 1,20-diacylated product can be used for the subsequent step as the acylated group will eventually be removed in the next step. In case of using acetic anhydride, the acylation reaction is completed by warming the reaction mixture (at 50–80°C) for 1–2 hours, although the condition may be varied according to the sorts of acylating agent. The resultant crude product is isolated by removing the excess acylating agent and the solvent under reduced pressure and may be purified, if desired, by way of column chromatography on silica gel.

In the third step for nitration, 1-N-acetyl-20-O-acetyl-1,2,6,7-tetrahydrocamptothecin obtained in the second step is dissolved in concentrated sulfuric acid and treated with fuming nitric acid under cooling for 20–40 minutes. The crude product is isolated by diluting the reaction mixture with ice water, extracting the organic phase with an organic solvent and evaporating the solvent under reduced pressure, and may be purified by way of column chromatography on silica gel. Although nitro group cannot be introduced into 10-position of camptothecin by directly nitrating camptothecin itself under the same conditions as described above, nitro group can selectively be introduced into 10-position of camptothecin according to the process of this invention by once converting it into 1-acyl-1,2,6,7-tetrahydrocamptothecin. The nitrated compound is then subjected to hydrolysis under an acidic or alkaline condition in a conventional manner to split off the acyl group. For this purpose, the nitrated compound is refluxed for several hours in a diluted mineral acid or a weak alkaline solution. The reaction mixture is then diluted with water or ice water and the water-insoluble deacylated product is extracted with a water-immiscible solvent and isolated by evaporating the solvent under reduced pressure. The hydrolyzed compound is then subjected to oxidation for dehydrogenation of the hydrogenated ring to the original aromatic ring. This oxidation itself is carried

out in a known conventional manner using DDQ (dichlorodicyanobenzoquinone), air, nitric acid or the like oxidizing agent. The use of DDQ is preferable and the reaction can be conducted by refluxing the mixture for about one hour. The end product can be isolated in a pure form by concentrating the reaction mixture under reduced pressure, extracting the residue with a solvent and evaporating the solvent under reduced pressure.

10-Nitrocampthothecin thus obtained can further be modified, if desired, to convert the nitro group into other functional substituents. If necessary, such modification of the nitro group may be carried out for the intermediately formed 1-acetyl-10-nitro-1,2,6,7-tetrahydrocampthothecin or 10-nitro-1,2,6,7-tetrahydrocampthothecin prior to hydrolysis followed by oxidation (dehydrogenation of the saturated ring) or oxidation, respectively.

In order to obtain the product of the general formula (I') wherein R<sup>3</sup> is amino group, 10-nitrocampthothecin, its tetrahydro derivative or its 1-acyl-tetrahydro derivative is subjected to a conventional reductive reaction contemplated for reducing nitro group to amino group. Usually, Clemensen's reduction method (a combination of a diluted mineral acid and tin, iron or zinc) or catalytic reduction method is used for this purpose. Advantageously, 10-nitrocampthothecin is dissolved in a solvent and hydrogenated at room temperature under atmospheric pressure in the presence of a small amount of platinum oxide. In this case, 10-aminocampthothecin aimed at can be obtained by removing the catalyst from the reaction mixture by filtration and evaporating the solvent under reduced pressure.

10-Aminocampthothecin or its tetrahydro derivative thus obtained can further be modified in various ways. In one embodiment, 10-aminocampthothecin or its derivative is alkylated in a conventional manner with an N-alkylating agent. As an alternative method, 10-aminocampthothecin or its derivative may first be acylated with an alkanoyl halide or alkanoyl anhydride and then reducing the carbonyl group in the resultant 10-alkanoylaminocampthothecin in a conventional manner.

In another embodiment, the 10-amino compound (10-aminocampthothecin or its tetrahydro derivative) is treated with a variety of acylating agents in accordance with a conventional method for acylating the free amino group to obtain 10-acylaminocampthothecin. For this purpose, various kinds of acylating agents such as acid anhydrides and acid halides of aliphatic, especially fatty acids with 1—18, preferably 1—8 carbon atoms, e.g. acetyl chloride, acetic anhydride, propionyl chloride, and butyric anhydride; of aromatic and heterocyclic acids, e.g. benzoyl chloride and nicotinoyl chloride; of aralkanoic acids, e.g. phenylacetyl chloride; and of aliphatic and aromatic sulfonic acid, e.g. ethanesulfonyl chloride and p-toluenesulfonyl chloride, come into question. The acylation can advantageously be carried out by treating 10-aminocampthothecin in a solvent with such acylating agent in the presence of an acid-binding agent such as pyridine.

In still another embodiment, the 10-amino compound is treated with a nitrite in an aqueous acidic medium to form the corresponding diazonium salt, which is then hydrolyzed under heating to form 10-hydroxycampthothecin. The diazotization of the 10-amino compound can be carried out in a conventional manner by adding an aqueous solution of a nitrite slowly to an acidic solution of 10-amino compound under stirring and ice cooling. After completion of the diazotization, the mixture is heated to cause hydrolysis of 10-diazonium salt whereby the corresponding 10-hydroxy compound is obtained. Likewise, the 10-diazonium salt can be treated with methanol to cause methanolysis thereby forming 10-methoxy compound. 10-Hydroxycampthothecin, and 10-methoxy- and 10-acetoxy campthothecin are already known as extracts from *Campthotheca acuminata* but could for the first time be synthesized from campthothecin by the present inventors.

In further embodiment, the 10-diazonium salt derived from the corresponding 10-amino compound is treated in an acidic medium with cuprous halide according to the so-called Sandmeyer reaction to form the corresponding 10-halogeno compound. In the preparation of 10-chlorocampthothecin, for example, an ice-cooled solution of the 10-diazonium chloride is slowly added dropwise to a warm acidic solution of cuprous chloride. Likewise, 10-bromocampthothecin can be prepared from a combination of the 10-diazonium bromide and cuprous bromide.

The compounds of the general formula (I) and those prepared for the first time according to the process of this invention can further be modified, if desired, by converting their 5-, 7- and/or 10-substituent into the other substituent according to a method known per se. For example, the free hydroxyl group in any of the 5-, 7- and 10-positions of the end product may be acylated or alkylated in a conventional manner to form modified compounds which are still involved in the compounds represented by the general formula (I).

The end products obtained according to the process of this invention can be used as such without further purification as active ingredients for medicaments or as valuable intermediate products for preparing other useful products.

Thus, the present invention is of particular significance in developing 10-substituted campthothecin derivatives as a new class of campthothecin derivatives which are useful as anti-tumor agents possessing anti-tumor activity with reduced toxicity and also as intermediate products for preparing other useful products as well as a new process for preparing these campthothecin derivatives in simple industrially advantageous operations.

The invention includes a new campthothecin derivative as defined above or prepared by any of the process of the invention for use in producing an anti-tumor effect in man or any other animal.

The invention further provides a pharmaceutical or veterinary formulation comprising a new camptothecin derivative as defined above or prepared by either of the processes of the invention, in either case formulated for pharmaceutical or veterinary use, respectively. The formulations of the invention can be in unit dosage form in accordance with normal practice and/or may comprise one or more acceptable diluents, carriers or excipients.

The present invention will now be illustrated in more detail by way of Examples. In these Examples, percentages are by weight unless otherwise indicated.

#### Example 1

##### 10 (A) Preparation of camptothecin-1-oxide:

Camptothecin (1.04 g, 3 m-mol) is suspended in acetic acid (100 ml). To this suspension is added 30% hydrogen peroxide (15 ml), and the mixture is stirred for 3 hours at 60–70°C. The resultant reaction mixture is concentrated under reduced pressure to a volume of about 35 ml and the concentrate was then poured into ice water (500 ml). The precipitated yellowish orange needle crystals are collected by filtration, washed  
15 with water and then with methanol and dried under reduced pressure whereby 866 mg (yield: 90.6%) of camptothecin-1-oxide is obtained. M.P. 254°C (dec.)

##### (B) Preparation of 10-[(carboethoxymethyl)thio]camptothecin:

Camptothecin-1-oxide (75 mg, 0.206 m-mol) obtained in the preceding (A) is dissolved in ethanol-free  
20 chloroform (50 ml) and dioxane (50 ml). To this solution are added boron trifluoride (50 µl) and ethyl thioglycolate (5 g), and the mixture is subjected to irradiation of light beam for 40 minutes. The reaction mixture is concentrated under reduced pressure. Water (100 ml) is then added to the concentrate and the mixture is extracted with chloroform (100 ml × 3). The chloroform phase is dried over magnesium sulfate, filtered and evaporated until dryness under reduced pressure. The residue is decolorized with silica gel (5  
25 g) and subjected to purification by way of high pressure liquid chromatography (Lichrosorb SI—60 column, 10% acetone-chloroform) whereby 20 mg (20.8%) of the title compound is obtained together with 22 mg of camptothecin. Yellow needle crystals, M.P. 228–231°C (dec.) (chloroform-*n*-hexane).

NMR (in CDCl<sub>3</sub>): 1.04 (3H, t, J=7.8Hz), 1.25 (3H, t, J=7.3Hz), 1.90 (2H, q, J=7.8Hz) 3.81 (2H, s), 4.21 (2H, q, J=7.3Hz), 5.28 (1H, d, J=16.6Hz), 5.27 (2H, s), 5.75 (2H, d, J=16.6Hz), 7.64 (1H, s), 7.70 (2H, m), 8.17 (1H, d,  
30 J=9Hz), 8.26 (1H, br s).

MS: m/e 466 [M<sup>+</sup>] (C<sub>24</sub>H<sub>22</sub>N<sub>2</sub>O<sub>6</sub>S = 466).

#### Example 2

##### Preparation of 10-methoxycamptothecin:

Camptothecin-1-oxide (75 mg, 0.206 m-mol) obtained in the preceding Example 1(A) is dissolved in  
35 methanol (50 ml) and dioxane (50 ml). To this solution is added conc. sulfuric acid (0.1 ml), and the mixture is subjected to irradiation of light beam (high voltage mercury lamp, 250W) for 25 minutes. The reaction mixture is concentrated under reduced pressure, diluted with water (100 ml) and extracted with chloroform (100 ml × 3). The chloroform phase is dried over magnesium sulfate, filtered and evaporated under  
40 reduced pressure until dryness. To the residue are added acetic anhydride (0.5 ml) and pyridine (1 ml), and the mixture is stirred for 1.5 hours at 60–70°C. The reaction mixture is evaporated until dryness under reduced pressure. The residue is decolorized with silica gel (5 g) and subjected to high pressure liquid chromatography (HPLC) using Richrosorb SI—60 column, 4% acetone-chloroform whereby 20-O-acetyl-  
45 camptothecin (7 mg) and 20-O-acetyl-10-methoxycamptothecin (37 mg, m/e 420[M<sup>+</sup>] C<sub>23</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub> = 20) are obtained. The latter compound is dissolved in conc. hydrochloric acid (2 ml) and methanol (1 ml) and the solution is stirred for 16 hours at room temperature. The reaction mixture is diluted with water (200 ml) and extracted with chloroform (200 ml). The chloroform phase is dried with magnesium sulfate, filtered and evaporated until dryness under reduced pressure whereby 28 mg (37.8%) of 10-methoxycamptothecin is  
50 obtained. M.P. 252–254°C (the value reported in literatures: m.p. 254–255°C). This compound was identified with a standard substance isolated from *Camptotheca acuminata* Nyssaceae, by way of HPLC and IR absorption spectra.

#### Example 3

##### Preparation of 10-hydroxycamptothecin:

Camptothecin-1-oxide (500 mg, 1.37 m-mol) obtained in the preceding Example 1(A) is dissolved in  
55 dioxane-acetonitrile-water (5:4:1, 500 ml). To this solution is added conc. sulfuric acid (1 ml), and the mixture is subjected to irradiation of light beam for 90 minutes. The reaction mixture is concentrated under reduced pressure and diluted with water (1l). The precipitate is collected by filtration and dried, and the resultant crude crystals are washed with methanol and purified by way of column chromatography on  
60 silica gel whereby 441 mg (yield: 88.2%) of 10-hydroxycamptothecin is obtained. This compound was identified with a standard substance isolated from *Camptotheca acuminata* Nyssaceae, by way of various spectral data.



## Example 4

## Preparation of 10-acetoxycamptothecin:

Camptothecin-1-oxide (75 mg, 0.206 m-mol) obtained in the preceding Example 1(A) is dissolved in acetic acid (100 ml) and the solution is subjected to irradiation of light beam for 45 minutes. The reaction mixture is evaporated until dryness under reduced pressure and the residue is decolorized with silica gel (5 g) and purified by way of HPLC (Richrosorb SI-60 column, 10% acetone-chloroform) whereby 26 mg (yield: 31.1%) of 10-acetoxycamptothecin is obtained as light yellowish white crystals together with 27.5 mg of camptothecin. The former compound is identical in HPLC and various spectral data with a standard substance obtained by treating 10-hydroxycamptothecin isolated from *Camptotheca acuminata* Nyssaceae with acetic anhydride in pyridine.

## Example 5

## (A) Preparation of 5-methylcamptothecin-1-oxide:

5-Methylcamptothecin (362 mg, 1 m-mol) is dissolved in acetic acid (25 ml). To this solution is added 30% hydrogen peroxide (2.5 ml, 0.0245 mol), and the mixture is warmed for 3 hours at 65–70°C. The reaction mixture is concentrated under reduced pressure to a volume of about one fifth and diluted with ice water (250 ml). The precipitated yellowish orange needle crystals are collected by filtration and dried at 60°C for 6 hours under reduced pressure whereby 234 mg (yield: 62.0%) of 5-methylcamptothecin-1-oxide is obtained. M.P. 226°C– (dec.)

MS: m/e 378 [M<sup>+</sup>] (C<sub>21</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub> = 378).

## (B) Preparation of 10-hydroxy-5-methylcamptothecin:

5-Methylcamptothecin-1-oxide (27 mg, 0.0714 m-mol) obtained in the preceding (A) is dissolved in acetonitrile (20 ml)-dioxane (25 ml)-water (5 ml). To this solution is added conc. sulfuric acid (50 μl), and the mixture is subjected to irradiation of light beam for 30 minutes. The reaction mixture is concentrated under reduced pressure and diluted with water (50 ml). The insoluble matter is collected by filtration, dried and purified by column chromatography on silica gel (2% methanol-chloroform) whereby 11 mg (yield: 50.6%) of the title end product is obtained as light yellowish white crystals together with 5 mg of 5-methylcamptothecin.

NMR (in DMSO-d<sub>6</sub>)δ: 0.87 (3H, t, J=7Hz), 1.77 (3H, br d, J=6Hz, C<sub>6</sub>-CH<sub>3</sub>), 1.84 (2H, q, J=7Hz), 5.36 (2H, br s, C<sub>17</sub>-H<sub>2</sub>), 5.60 (1H, m, C<sub>8</sub>-H), 6.43 (1H, br s, D<sub>2</sub>O-exchangeable), 7.07 (2H, m, C<sub>9</sub>-H and C<sub>14</sub>-H), 7.14 (1H, d x d, J=9Hz, 2Hz, C<sub>11</sub>-H), 7.84 (1H, d, J=9Hz, C<sub>12</sub>-H), 8.41 (1H, br s, C<sub>7</sub>-H), 10.34 (1H, s, D<sub>2</sub>O-exchangeable).

MS: m/e 378 [M<sup>+</sup>] (C<sub>21</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub> = 378).

## Example 6

## (A) Preparation of 5-methoxycamptothecin-1-oxide:

5-Methoxycamptothecin (190 mg, 0.5 m-mol) is dissolved in acetic acid (15 ml). To this solution is added 30% hydrogen peroxide (1.25 ml, 0.0125 mol), and the mixture is stirred for 3 hours at 65–70°C. The reaction mixture is concentrated under reduced pressure to a volume of about one fourth and diluted with ice water (200 ml). The precipitated yellowish orange needle crystals are collected by filtration and then dried under reduced pressure for 6 hours at 60°C whereby 145 mg (yield: 73.6%) of 5-methoxycamptothecin-1-oxide is obtained. M.P. 208°C– (dec.)

NMR (in CDCl<sub>3</sub>): 1.03 (3H, t, J=7Hz), 1.92 (2H, q, J=7Hz), 3.51, 3.66 (1.5H x 2, s, s), 5.30 (1H, d, J=16Hz), 5.59 (1H, d, J=16Hz), 6.73, 6.85 (0.5H x 2, s, s), 7.72–8.01 (4H, m), 8.24 (1H, s), 8.76 (1H, m).

MS: m/e 394 [M<sup>+</sup>] (C<sub>21</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub> = 394).

## (B) Preparation of 10-hydroxy-5-methoxycamptothecin:

5-Methoxycamptothecin-1-oxide (98 mg, 0.248 m-mol) is dissolved in acetonitrile (50 ml)-dioxane (50 ml)-water (5 ml). To this solution is added conc. sulfuric acid (100 μl), and the mixture is subjected to irradiation of light beam for 30 minutes. The reaction mixture is concentrated under reduced pressure and diluted with water (100 ml). The insoluble matter is collected by filtration, dried and purified by column chromatography on silica gel (2% methanol-chloroform) whereby 23.5 mg (yield: 26.1%) of the title end product is obtained together with 5-methoxycamptothecin.

NMR (in DMSO-d<sub>6</sub>)δ: 0.87 (3H, t, J=7Hz), 1.83 (2H, q, J=7Hz), 3.46, 3.54 (1.5H x 2, s, s, C<sub>6</sub>-OCH<sub>3</sub>), 5.39 (2H, br s, C<sub>17</sub>-H), 6.28 (1H, br s, D<sub>2</sub>O-exchangeable), 6.80, 6.86 (0.5H x 2, s, s, C<sub>8</sub>-H), 7.02 (1H, d, J=2Hz, C<sub>9</sub>-H), 7.21 (1H, br s, C<sub>14</sub>-H), 7.25 (1H, d, d, J=9Hz, 2Hz, C<sub>11</sub>-H), 7.90 (1H, d, J=9Hz, C<sub>12</sub>-H), 8.48 (1H, br s, C<sub>7</sub>-H), 10.36 (1H, s, D<sub>2</sub>O-exchangeable).

MS: m/e 394 [M<sup>+</sup>] (C<sub>21</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub> = 394).

## Example 7

## (A) Preparation of 7-ethylcamptothecin-1-oxide:

7-Ethylcamptothecin (1.00 g, 2.65 m-mol) is dissolved in acetic acid (300 ml). To this solution is added 30% hydrogen peroxide (7.5 ml, 0.0736 mol), and the mixture is stirred for 3 hours at 65–70°C. The reaction mixture is concentrated under reduced pressure to a volume of about one fourth and diluted with ice water

(500 ml). The precipitated yellowish orange needle crystals are collected by filtration and dried for 6 hours at 60°C under reduced pressure whereby 808 mg (yield: 77.7%) of 7-ethylcamptothecin-1-oxide is obtained. M.P. 255°C— (dec.)

NMR (in DMSO- $d_6$ ): 0.87 (3H, t, J=7Hz), 1.28 (3H, t, J=7Hz), 1.84 (2H, q, J=7Hz), 3.10 (2H, q, J=7Hz), 5.26 (2H, s), 5.36 (2H, s), 6.24 (1H, s,  $D_2O$ -exchangeable), 7.80 (3H, m), 8.10 (1H, s), 8.35 (1H, m). MS: m/e 392 [ $M^+$ ] ( $C_{22}H_{20}N_2O_5$  = 392).

#### (B) Preparation of 7-ethyl-10-hydroxycamptothecin:

7-Ethylcamptothecin-1-oxide (100 mg, 0.255 m-mol) is dissolved in acetonitrile (65 ml)-dioxane (30 ml)-water (5 ml). To this solution is added conc. sulfuric acid (0.1 ml), and the mixture is subjected to irradiation of light beam for 25 minutes. The reaction mixture is concentrated under reduced pressure, diluted with water (100 ml) and extracted with chloroform (100 ml  $\times$  3). The chloroform phase is dried over magnesium sulfate, filtered and evaporated under reduced pressure until dryness. The residue is purified by column chromatography on silica gel (2% methanol-chloroform) whereby 43 mg (yield: 49.1%) of the title end product is obtained as light yellowish white crystals together with 12 mg of 7-ethylcamptothecin. M.P. 231°C— (dec.) [EtOH].

NMR (in  $CDCl_3$ ): 0.98 (3H, t, J=7Hz), 1.38 (3H, t, J=7Hz), 1.90 (2H, q, J=7Hz), 3.08 (2H, q, J=7Hz), 5.17 (2H, s), 5.23 (1H, d, J=16Hz), 5.54 (1H, d, J=16Hz), 7.34 (2H, m), 7.39 (1H, s), 7.92 (1H, d, J=9Hz). MS: m/e 392 [ $M^+$ ] ( $C_{22}H_{20}N_2O_5$  = 392).

20

#### Example 8

##### Preparation of 7-ethyl-10-methoxycamptothecin:

7-Ethylcamptothecin-1-oxide (100 mg, 0.255 m-mol) obtained in the preceding Example 7(A) is dissolved in methanol (50 ml)-dioxane (50 ml). To this solution is added conc. sulfuric acid (0.1 ml) and the mixture is subjected to irradiation of light beam for 30 minutes. The reaction mixture is concentrated under reduced pressure, diluted with water (100 ml) and extracted with chloroform (100 ml  $\times$  3). The chloroform phase is dried with magnesium sulfate, filtered and evaporated until dryness under reduced pressure. The residue is decolorized with silica gel (5 g) and purified by HPLC (Richrosorb Si—60 column, 10% acetone-chloroform) whereby 27 mg (yield: 33.2%) of the title end product is obtained together with 18 mg of 7-ethylcamptothecin. Light yellowish white needle crystals with M.P. 261°C— (dec.) [n-hexane-chloroform].

NMR (in  $CDCl_3$ ): 1.28 (3H, t, J=7Hz), 1.49 (3H, t, J=7Hz), 1.97 (2H, q, J=7Hz), 3.24 (2H, q, J=7Hz), 4.30 (3H, s), 5.27 (2H, s), 5.25 (1H, d, J=16Hz), 5.70 (1H, d, J=16Hz), 7.20 (1H, d, J=3Hz), 7.47 (1H, d  $\times$  d, J=9Hz, 3Hz), 7.72 (1H, s), 8.53 (1H, d, J=9Hz).

MS: m/e 406 [ $M^+$ ] ( $C_{23}H_{22}N_2O_5$  = 406).

35

#### Example 9

##### (A) Preparation of 7-propylcamptothecin-1-oxide:

7-Propylcamptothecin (390 mg, 1 m-mol) is dissolved in acetic acid (55 ml). To this solution is added 30% hydrogen peroxide (3 ml, 0.0294 m-mol), and the mixture is stirred for 4 hours at 65—70°C. The reaction mixture is concentrated under reduced pressure to a volume of about 10 ml and diluted with ice water (250 ml). The precipitated yellowish orange needle crystals are collected by filtration and dried for 6 hours at 60°C under reduced pressure whereby 278 mg (yield: 68.4%) of 7-propylcamptothecin-1-oxide is obtained. M.P. 238°C— (dec.)

MS: m/e 406 [ $M^+$ ] ( $C_{23}H_{22}N_2O_5$  = 406).

45

##### (B) Preparation of 10-hydroxy-7-propylcamptothecin:

7-Propylcamptothecin-1-oxide (200 mg, 0.493 m-mol) obtained in the preceding (A) is dissolved in dioxane (60 ml)-acetonitrile (20 ml)-water (5 ml). To this solution is added conc. sulfuric acid (100  $\mu$ l), and the mixture is subjected to irradiation of light beam for 30 minutes. The reaction mixture is concentrated under reduced pressure and diluted with water (100 ml). The insoluble matter is collected by filtration, dried and purified by column chromatography on silica gel (2% methanol-chloroform) whereby the title end product (121 mg, yield: 60.5%) is obtained together with 11 mg of 7-propylcamptothecin. Light yellowish white needle crystals with M.P. 237°C— (dec.) [toluene].

NMR (in DMSO- $d_6$ ): 0.89 (3H, t, J=7Hz), 1.06 (3H, t, J=7Hz), 1.60—1.90 (5H, m), 3.00 (2H, t, J=7Hz), 5.24 (2H, s), 5.40 (2H, s), 6.24 (1H, s,  $D_2O$ -exchangeable), 7.35 (1H, s), 7.30 (2H, m), 7.99 (1H, d, J=9Hz). MS: m/e 406 [ $M^+$ ] ( $C_{23}H_{22}N_2O_6$  = 406).

55

#### Example 10

##### (A) Preparation of 7-benzylcamptothecin-1-oxide:

7-Benzylcamptothecin (250 mg, 0.570 m-mol) is dissolved in acetic acid (50 ml). To this solution is added 30% hydrogen peroxide (2 ml, 0.0196 mol), and the mixture is stirred for 3 hours at 65—70°C. The reaction mixture is concentrated under reduced pressure to a volume of about 10 ml and then diluted with ice water (250 ml). The precipitated yellowish orange needle crystals are collected by filtration and dried for 6 hours at 60°C under reduced pressure whereby 164 mg (yield: 63.5%) of 7-benzylcamptothecin-1-oxide is obtained. M.P. 220°C— (dec.)

65

NMR (in  $\text{CDCl}_3$ ): 1.09 (3H, t,  $J=7.5\text{Hz}$ ), 1.87 (2H, q,  $J=7.5\text{Hz}$ ), 4.48 (2H, s), 5.16 (2H, s), 5.20 (1H, d,  $J=16\text{Hz}$ ), 5.64 (1H, s,  $J=16\text{Hz}$ ), 7.05–8.12 (8H, m), 8.32 (1H, s), 8.80 (1H, m).  
 MS:  $m/e$  454 [ $\text{M}^+$ ] ( $\text{C}_{27}\text{H}_{22}\text{N}_2\text{O}_5 = 454$ ).

5 (B) Preparation of 10-acetoxy-7-benzylcamptothecin:

7-Benzylcamptothecin-1-oxide (100 mg, 0.22 m-mol) obtained in the preceding (A) is dissolved in acetic acid (100 ml) and the solution is subjected to irradiation of light beam for one hour. The reaction mixture is evaporated under reduced pressure until dryness. The residue is decolorized with silica gel (5 g) and purified by HPLC (Richlosorb SI—60 column, 4% acetone-chloroform) whereby 28 mg (yield: 29.9%) of the title end product is obtained together with 14 mg of 7-benzylcamptothecin. The product is recrystallized from *n*-hexane-chloroform to afford light yellowish white needle crystals. M.P.  $226^\circ\text{C}$ —(dec.).

10 NMR (in  $\text{CDCl}_3$ ): 1.03 (3H, t,  $J=7.3\text{Hz}$ ), 1.85 (2H, q,  $J=7.3\text{Hz}$ ), 2.37 (3H, s), 4.52 (2H, s), 5.11 (2H, s), 5.26 (1H, d,  $J=16\text{Hz}$ ), 5.73 (1H, d,  $J=16\text{Hz}$ ), 7.10 (5H, m), 7.53 (1H, d x d,  $J=9\text{Hz}$ , 3Hz), 7.65 (1H, s), 7.89 (1H, d,  $J=3\text{Hz}$ ), 8.27 (1H, d,  $J=9\text{Hz}$ ).

15 MS:  $m/e$  496 [ $\text{M}^+$ ] ( $\text{C}_{29}\text{H}_{24}\text{N}_2\text{O}_6 = 496$ ).

Example 11

(A) Preparation of 7-acetoxymethylcamptothecin-1-oxide:

7-Acetoxymethylcamptothecin (1.0 g, 2.38 m-mol) is dissolved in acetic acid (150 ml). To this solution is added 30% hydrogen peroxide (10 ml, 0.0981 mol), and the mixture is stirred for 3.5 hours at  $65$ – $70^\circ\text{C}$ . The reaction mixture is concentrated under reduced pressure to a volume of about 50 ml, diluted with ice water (350 ml) and extracted with chloroform (300 ml x 3). The chloroform phase is washed with a 7% aqueous solution of sodium hydrogen carbonate, dried over magnesium sulfate and dried until dryness under reduced pressure. The residue is purified by reprecipitation with chloroform-*n*-hexane whereby 679 mg (yield: 65.9%) of 7-acetoxymethylcamptothecin-1-oxide is obtained as yellow needle crystals. M.P.  $250^\circ\text{C}$ —(dec.).

25 NMR (in  $\text{DMSO}-d_6$ ): 0.87 (3H, t,  $J=7\text{Hz}$ ), 1.83 (2H, q,  $J=7\text{Hz}$ ), 2.05 (3H, s), 5.42 (4H, br s), 5.61 (2H, s), 6.42 (1H, s,  $\text{D}_2\text{O}$ -exchangeable), 7.80 (2H, m), 7.91 (1H, s), 8.20 (1H, m), 8.63 (1H, m).

MS:  $m/e$  436 [ $\text{M}^+$ ] ( $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_7 = 436$ ).

30 (B) Preparation of 7-acetoxymethyl-10-hydroxycamptothecin:

7-Acetoxymethylcamptothecin-1-oxide (75 mg, 0.172 m-mol) obtained in the preceding (A) is dissolved in dioxane (40 ml)-acetonitrile (50 ml)-water (10 ml). To this solution is added conc. sulfuric acid (0.1 ml), and the mixture is subjected to irradiation of light beam for 45 minutes. The reaction mixture is concentrated under reduced pressure to about half a volume, diluted with water (100 ml) and extracted with chloroform (200 ml x 2). The chloroform phase is dried over magnesium sulfate, filtered and evaporated until dryness under reduced pressure. The residue is separated by way of column chromatography on silica gel (2% methanol-chloroform) whereby 24 mg (yield: 32%) of the title end product is obtained together with 7-acetoxymethylcamptothecin (22 mg). Light yellowish white needle crystals, M.P.  $257^\circ\text{C}$  (dec.) [*n*-hexane-chloroform].

40 NMR (in  $\text{DMSO}-d_6$ ): 0.98 (3H, t,  $J=7\text{Hz}$ ), 1.38 (3H, t,  $J=7\text{Hz}$ ), 1.90 (2H, q,  $J=7\text{Hz}$ ), 3.08 (2H, q,  $J=7\text{Hz}$ ), 5.17 (2H, s), 5.23 (2H, s), 5.54 (2H, s), 6.34 (1H, br,  $\text{D}_2\text{O}$ -exchangeable), 7.34 (2H, m), 7.39 (1H, s), 7.92 (1H, d,  $J=9\text{Hz}$ ).

MS:  $m/e$  436 [ $\text{M}^+$ ] ( $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_7 = 436$ ).

45

Example 12

(A) Preparation of 7-hydroxymethylcamptothecin-1-oxide:

7-Hydroxymethylcamptothecin (300 mg, 0.794 m-mol) is suspended in glacial acetic acid (70 ml). To this suspension is added 30% hydrogen peroxide (30 ml), and the mixture is stirred for one hour at  $70$ – $80^\circ\text{C}$ . 30% Hydrogen peroxide (20 ml) is added and the mixture is further stirred for 1.5 hours at  $70$ – $80^\circ\text{C}$ . The reaction mixture is concentrated under reduced pressure to a volume of 40 ml. Ice water (60 ml) is added to the concentrate and the mixture is allowed to stand for 12 hours. The precipitated yellow crystals are collected by filtration and dried under reduced pressure whereby 142 mg (yield: 45.4%) of the title compound is obtained as yellow needle crystals. M.P.  $255$ – $260^\circ\text{C}$  (dec.).

55 IR  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 3400, 2940, 1755, 1650, 1600, 1460, 1160, 1100, 765.

(B) Preparation of 7-hydroxymethyl-10-hydroxycamptothecin:

7-Hydroxymethylcamptothecin-1-oxide (50 mg, 0.127 m-mol) obtained in the preceding (A) is dissolved in a solvent mixture of dioxane (40 ml), acetonitrile (40 ml) and water (10 ml). To this solution is added conc. sulfuric acid (3 drops), and the mixture is subjected to irradiation of light beam for 10 minutes. The reaction mixture is concentrated under reduced pressure and water (20 ml) is added to the residue. The insoluble matter is collected by filtration and dried to obtain 40 mg (80%) of the title compound is obtained, which is purified by chromatography on silica gel. M.P.  $260$ – $263^\circ\text{C}$  (dec.).

IR  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 3400, 2980, 1735, 1650, 1590, 1240, 1160, 1100, 800, 775.

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## Example 13

## (A) Preparation of 1,2,6,7-tetrahydrocamptothecin:

Camptothecin (500 mg, 1.43 m-mol) is suspended in acetic acid (100 ml). Platinum oxide (100 mg) is added to the suspension and the mixture is subjected to catalytic reduction (1.5 hours, absorption of about 140 ml of hydrogen) at room temperature under atmospheric pressure. After removing the catalyst by filtration, the reaction mixture is evaporated until dryness under reduced pressure. The residue is taken up in chloroform (200 ml) and washed with a 5% aqueous solution of sodium hydrogen carbonate (100 ml) and then with a saturated solution of sodium chloride (100 ml). The chloroform phase is dried over magnesium sulfate, filtered and evaporated under reduced pressure until dryness. The residue is purified by column chromatography (chloroform) on silica gel (20 g) whereby 285 mg (conversion rate: 56.3%; yield: 76.7%) of the title compound is obtained as yellowish white crystals. Unreacted starting materials (113 mg in crude state) is recovered. M.P. (dec.) 240—242°C (from methanol).  
IR  $\nu_{\text{max}}^{\text{KBr}}$ , cm<sup>-1</sup>: 3470, 1745, 1645, 1565, 1495, 1165, 1030.

## 15 (B) Preparation of 1,20-O-diacetyl-1,2,6,7-tetrahydrocamptothecin:

Camptothecin (500 mg, 1.43 m-mol) is suspended in acetic acid (100 ml). Platinum oxide (100 mg) is added to the suspension and the mixture is subjected to catalytic reduction (1.5 hours at room temperature, absorption of about 140 ml of hydrogen) under atmospheric pressure. After removing the catalyst by filtration, the reaction mixture is evaporated until dryness under reduced pressure. The residue is taken up in pyridine (5 ml) and acetic anhydride (1 ml) is added. The mixture is warmed at 60—65°C for 1.5 hours and the reaction mixture is evaporated until dryness under reduced pressure. The residue is purified by column chromatography on silica gel (2% acetone-chloroform) whereby 349 mg (yield: 76.7%) of the title compound is obtained and 149 mg of crude 20-O-acetylcamptothecin is recovered. Colorless needle crystals, M.P. >280°C (from C<sub>6</sub>H<sub>6</sub>).

25 NMR (in CDCl<sub>3</sub>) $\delta$ : 0.78 (3H, t, J=7Hz, —CH<sub>2</sub>CH<sub>3</sub>), 2.18 (2H, m, —CH<sub>2</sub>CH<sub>3</sub>), 2.20 (6H, s, 20—O—COCH<sub>3</sub> + N—1—COCH<sub>3</sub>), 2.80 (2H, br m, C—7—H<sub>2</sub>), 3.50 (2H, br m, C—5—H<sub>2</sub>), 4.10 (1H, m, C—6—H), 5.02, 5.38 (1H, 1H, d x d, J=17Hz, C—17—H<sub>2</sub>), 7.20 (1H, s, C—14—H), 7.24 (1H, m, C—2—H), 7.69 (1H, m), 8.10 (3H, m).

MS: m/e 432 [M<sup>+</sup>] C<sub>24</sub>H<sub>24</sub>N<sub>2</sub>O<sub>6</sub>=432.

## 30 (C) Preparation of 1-acetyl-10-nitro-1,2,6,7-tetrahydrocamptothecin:

Camptothecin (500 mg, 1.44 m-mol) is suspended in a solvent mixture of glacial acetic acid (50 ml) and dioxane (50 ml). Platinum oxide (100 mg) is added to the suspension and the mixture is subjected to catalytic reduction at room temperature under atmospheric pressure for one hour. The catalyst is removed by filtration and the solvents are removed by distillation under reduced pressure. The residue is dissolved in chloroform (200 ml) and the solution is washed with a 5% aqueous solution of sodium hydrogen carbonate (50 ml). The chloroform phase is separated, dried over MgSO<sub>4</sub> and distilled under reduced pressure to remove the solvent. The above operation is repeated 6 times and the resultant 6 lots of products are blended with celite and then subjected to column chromatography on silica gel (eluent: ethyl acetate) whereby 1,2,6,7-tetrahydrocamptothecin is obtained. To this compound are added 5 ml of pyridine and 5 ml of acetic anhydride, and the mixture is warmed at 60°C for one hour. The pyridine and the acetic anhydride are eliminated by distillation under reduced pressure and the residue is taken up in chloroform (300 ml) and washed with a 5% aqueous solution of hydrochloric acid and then with a 5% aqueous solution of sodium hydrogen carbonate. The chloroform phase is dried over MgSO<sub>4</sub> and the chloroform is removed by distillation under reduced pressure whereby 1-acetyl-20-O-acetyl-1,2,6,7-tetrahydrocamptothecin is obtained. This compound is dissolved in 50 ml of conc. sulfuric acid. Fuming nitric acid (0.9 ml) is added to the solution under ice cooling and the mixture is stirred for 30 minutes and poured into ice water (about 300 ml). The mixture is extracted with chloroform (200 ml x 3) and the chloroform extract is dried with MgSO<sub>4</sub>. The chloroform is removed by distillation under sub-atmospheric pressure and the residue is blended with celite and subjected to column chromatography on silica gel (eluent: 1% MeOH—CHCl<sub>3</sub>) whereby 1.75 g (yield: 46.2% from camptothecin) of 1-acetyl-10-nitro-1,2,6,7-tetrahydrocamptothecin is obtained. Light yellowish white needle crystals, M.P. (with decomp.) 271—273°C (from AcOEt).

55 NMR (in DMSO-d<sub>6</sub>) $\delta$ : 0.63 (3H, t, J=7Hz, —CH<sub>2</sub>CH<sub>3</sub>), 1.63 (2H, q, J=7Hz, —CH<sub>2</sub>CH<sub>3</sub>), 2.23 (3H, s, N—1—COCH<sub>3</sub>), 2.8—3.0 (2H, br, m), 3.4—3.8 (3H, br, m), 4.0—4.2 (1H, br, m), 5.10 (2H, s, C—17—H), 6.26 (1H, s, C—20—OH), 6.43 (1H, s, C—14—H), 7.53 (1H, d, J=9Hz, C—12—H), 8.03 (1H, d, d, J=9Hz, 2Hz, C—11—H), 8.22 (1H, d, J=2Hz, C—9—H).

IR  $\nu_{\text{max}}^{\text{KBr}}$ , cm<sup>-1</sup>: 3450, 1755, 1660, 1585, 1525, 1375, 1345, 1300, 1155.

MS: m/e 439 [M<sup>+</sup>] C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O<sub>7</sub>=439.

## 60 (D) Preparation of 10-nitro-1,2,6,7-tetrahydrocamptothecin:

1-Acetyl-10-nitro-1,2,6,7-tetrahydrocamptothecin (500 mg, 1.14 m-mol) is dissolved in a 20% aqueous solution of sulfuric acid (30 ml) and the solution is boiled under reflux for 2 hours. The reaction mixture is diluted with ice water (200 ml) and extracted with chloroform (200 ml x 3). The chloroform phase is dried over magnesium sulfate, filtered and evaporated until dryness under reduced pressure whereby 373 mg

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(yield: 82.3%) of the title compound is obtained as yellow crystals. M.P. (with decomp.) 274—275°C (from  $\text{CHCl}_3$ ).

IR  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 3480, 1785, 1655, 1610, 1585, 1510, 1315, 1290, 1260.

MS:  $m/e$  397 [ $\text{M}^+$ ]  $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_6=397$ .

(E) Preparation of 10-nitrocamptothecin:

10-Nitro-1,2,6,7-tetrahydrocamptothecin (373 mg, 0.937 m-mol) is dissolved in dioxane (30 ml). To this solution is added DDQ (446 mg, 1.968 m-mol), and the mixture is boiled under reflux for one hour. The reaction mixture is evaporated until dryness under reduced pressure and the residue is taken up in chloroform (300 ml) and washed with water (200 ml  $\times$  2). The chloroform phase is dried over magnesium sulfate, filtered and evaporated until dryness under reduced pressure whereby 340 mg (yield: 92.3%) of the title compound is obtained as yellow crystals. M.P. (with decomp.) 243—245°C (from chloroform).

NMR (in  $\text{DMSO}-d_6$ ) $\delta$ : 0.89 (3H, t,  $J=7\text{Hz}$ ,  $-\text{CH}_2\text{CH}_3$ ), 1.87 (2H, q,  $J=7\text{Hz}$ ,  $-\text{CH}_2\text{CH}_3$ ), 5.28 (2H, s, C—5—H), 5.42 (2H, s, C—17—H), 6.51 (1H, s, C—20—OH), 7.33 (1H, s, C—14—H), 7.83 (1H, d, d,  $J=9\text{Hz}$ , 2Hz, C—11—H), 8.16 (1H, d,  $J=9\text{Hz}$ , C—12—H), 8.25 (1H, d,  $J=2\text{Hz}$ , C—9—H), 8.64 (1H, s, C—7—H).

IR  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 3430, 1742, 1656, 1618, 1592, 1530, 1342, 1158.

MS:  $m/e$  393 [ $\text{M}^+$ ]  $\text{C}_{20}\text{H}_{18}\text{N}_3\text{O}_6=393$ .

Example 14

20 Preparation of 10-aminocamptothecin:

10-Nitrocamptothecin (108 mg, 0.275 m-mol) is dissolved in ethanol (30 ml) and dioxane (20 ml). To this solution is added platinum oxide (20 mg), and the mixture is subjected to catalytic reduction for 30 minutes at room temperature under normal pressure. The catalyst is removed by filtration and the reaction mixture is evaporated under reduced pressure until dryness whereby 96 mg (yield: 96.2%) of 10-amino-

camptothecin is obtained as a yellowish brown solid.

NMR (in  $\text{DMSO}-d_6$ ) $\delta$ : 0.88 (3H, t,  $J=7\text{Hz}$ ,  $-\text{CH}_2\text{CH}_3$ ), 1.86 (2H, q,  $J=7\text{Hz}$ ,  $-\text{CH}_2\text{CH}_3$ ), 5.17 (2H, s, C—5—H), 5.39 (2H, s, C—17—H), 6.90 (1H, d,  $J=2\text{Hz}$ , C—9—H), 7.19 (1H, s, C—14—H), 7.26 (1H, d, d,  $J=9\text{Hz}$ , 2Hz, C—11—H), 7.84 (1H, d,  $J=9\text{Hz}$ , C—12—H), 8.20 (1H, s, C—7—H).

MS:  $m/e$  363 [ $\text{M}^+$ ]  $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_4=363$ .

Example 15

Preparation of 10-hydroxycamptothecin:

10-Aminocamptothecin (50 mg, 0.138 m-mol) is dissolved in a 10% aqueous solution of sulfuric acid (5 ml). To this solution in a salted ice bath is added dropwise slowly an aqueous solution of sodium nitrite (9.5 mg, 0.138 m-mol) with stirring. After the addition of sodium nitrite, the mixture is further stirred for 10 minutes in a salted ice bath. To the reaction mixture is added conc. sulfuric acid (1 ml), and the whole is boiled under reflux for 2 hours. The reaction mixture is diluted with ice water (200 ml) and chloroform (200 ml) is added. The mixture is shaken in a separating funnel and the resultant emulsion is filtered through celite. The chloroform phase containing camptothecin formed as by-product by side reactions is dried over magnesium sulfate, filtered and evaporated until dryness under reduced pressure whereby camptothecin (8 mg) is recovered. On the other hand, a solid on the celite, which is insoluble in chloroform-water, is taken up in 20%  $\text{MeOH}-\text{CHCl}_3$  (200 ml) and the solution is evaporated until dryness under reduced pressure whereby 28 mg (yield: 66.5%) of the title compound is obtained as light yellow crystals. M.P. (with decomp.) 270—272°C (from pyridine-methanol).

NMR (in  $\text{DMSO}-d_6$ ) $\delta$ : 0.88 (3H, t,  $J=7\text{Hz}$ ,  $-\text{CH}_2\text{CH}_3$ ), 1.86 (2H, q,  $J=7\text{Hz}$ ,  $-\text{CH}_2\text{CH}_3$ ), 5.22 (2H, s, C—5—H), 5.40 (2H, s, C—17—H), 6.47 (1H, s, C—20—CH), 7.2 (2H, m, C—9—H and C—14—H), 7.41 (1H, d, d,  $J=9\text{Hz}$ , 2Hz, C—11—H), 8.01 (1H, d,  $J=9\text{Hz}$ , C—12—H), 8.43 (1H, s, C—7—H).

IR  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 3450, 1720, 1655, 1590, 1505, 1265.

Example 16

Preparation of 10-chlorocamptothecin:

1-Acetyl-10-nitro-1,2,6,7-tetrahydrocamptothecin (439 mg, 1.00 m-mol) obtained in Example 13(C) is dissolved in ethanol (30 ml) and dioxane (20 ml). To this solution is added platinum oxide (60 mg), and the mixture is subjected to catalytic reduction for 30 minutes at room temperature under normal pressure. The catalyst is removed by filtration and the reaction mixture is evaporated until dryness under reduced pressure whereby 1-acetyl-10-amino-1,2,6,7-tetrahydrocamptothecin (MS:  $m/e$  409 [ $\text{M}^+$ ]  $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_5=409$ ) is obtained. This compound is dissolved in 12% hydrochloric acid (8 ml). To this solution in a salted ice bath is added dropwise slowly an aqueous solution of sodium nitrite (104 mg, 1.5 m-mol) with stirring. After the addition of sodium nitrite, the mixture is further stirred for 15 minutes under cooling in the salted ice bath.

This reaction mixture is added dropwise to a solution of cuprous chloride (521 mg, 5.00 m-mol) in 17% hydrochloric acid (10 ml) warmed at 60—70°C under agitation. After the addition, the mixture is further agitated for one hour at 60—70°C. The reaction mixture is diluted with ice water (300 ml) and extracted with chloroform (200 ml  $\times$  2). The chloroform phase is dried over magnesium sulfate, filtered and evaporated until dryness under reduced pressure whereby 1-acetyl-10-chloro-1,2,6,7-tetrahydrocamptothecin (MS:  $m/e$  428 [ $\text{M}^+$ ], 430 [ $\text{M}+2$ ]  $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_5\text{Cl}=428.5$ ) is obtained. This compound is dissolved in a 30% aqueous

solution of sulfuric acid (20 ml) and the solution is boiled under reflux for 1.5 hours. The reaction mixture is diluted with ice water (200 ml) and extracted with chloroform (150 ml  $\times$  3). The chloroform phase is dried over magnesium sulfate, filtered and evaporated until dryness under reduced pressure to obtain 10-chloro-1,2,6,7-tetrahydrocamptothecin. This compound is dissolved in dioxane (30 ml) and DDQ (288 mg, 0.634 m-mol) is then added to the solution. The mixture is boiled under reflux for 1.5 hours and then evaporated until dryness under reduced pressure. The residue is dissolved in chloroform (300 ml) and washed with water (100 ml  $\times$  2). The chloroform phase is dried over magnesium sulfate, filtered and evaporated until dryness under reduced pressure whereby 184 mg (yield: 48.0% from 1-acetyl-10-nitro-1,2,6,7-tetrahydrocamptothecin) of the title compound is obtained as white crystals.

This end product can also be prepared from 10-aminocamptothecin by diazotization followed by substitution reaction with cuprous chloride (Sandmeyer reaction) in the same manner as described above. M.P. (with decomp.) 279–280°C (from  $\text{CHCl}_3$ ).

NMR (in  $\text{DMSO}-d_6$ )  $\delta$ : 0.89 (3H, t,  $J=7\text{Hz}$ ,  $-\text{CH}_2\text{CH}_3$ ), 1.87 (2H, q,  $J=7\text{Hz}$ ,  $-\text{CH}_2\text{CH}_3$ ), 5.28 (2H, s, C—5—H), 5.42 (2H, s, C—17—H), 6.51 (1H, s, C—20—OH), 7.33 (1H, s, C—14—H), 7.83 (1H, d, d,  $J=9\text{Hz}$ , 2Hz, C—11—H), 8.16 (1H, d,  $J=9\text{Hz}$ , C—12—H), 8.25 (1H, d,  $J=2\text{Hz}$ , C—9—H), 8.64 (1H, s, C—7—H).

$\text{IR}_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 3400, 1745, 1650, 1585, 1490, 1225, 1155.

MS:  $m/e$  382 [ $\text{M}^+$ ], 384 [ $\text{M}+2$ ]  $\text{C}_{20}\text{H}_{15}\text{N}_2\text{O}_4\text{Cl}=382$ .

#### Example 17

##### 20 Preparation of 10-bromocamptothecin:

1-Acetyl-10-nitro-1,2,6,7-tetrahydrocamptothecin (439 mg, 1.00 m-mol) obtained in Example 13(C) is dissolved in ethanol (30 ml) and dioxane (20 ml). To this solution is added platinum oxide (60 mg), and the mixture is subjected to catalytic reduction for 30 minutes at room temperature under normal pressure. The catalyst is filtered off and the reaction mixture is evaporated until dryness under reduced pressure whereby 1-acetyl-10-amino-1,2,6,7-tetrahydrocamptothecin (MS:  $m/e$  409 [ $\text{M}^+$ ]  $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_6=409$ ) is obtained. This compound is dissolved in 24% hydrobromic acid (10 ml). To this solution in a salted ice bath is added dropwise slowly an aqueous solution of sodium nitrite (104 mg, 1.50 m-mol) with stirring. After the addition of sodium nitrite, the mixture is continuously stirred for 15 minutes under cooling in the salted ice bath. The reaction mixture is added dropwise to a solution of cuprous bromide (717 mg, 5.00 m-mol) in 24% hydrobromic acid (10 ml) warmed at 60–70°C under agitation. After the addition, the mixture is continuously agitated for one hour at 60–70°C. The reaction mixture is diluted with ice water (200 ml) and extracted with chloroform (200 ml  $\times$  3). The chloroform phase is dried over magnesium sulfate, filtered and evaporated until dryness under reduced pressure whereby 1-acetyl-10-bromo-1,2,6,7-tetrahydrocamptothecin (MS:  $m/e$  472 [ $\text{M}^+$ ], 474 [ $\text{M}+2$ ]  $\text{C}_{22}\text{H}_{21}\text{N}_2\text{O}_6\text{Br}=473$ ) is obtained. This compound is dissolved in a 30% aqueous solution of sulfuric acid (20 ml) and the solution is boiled under reflux for one hour. The reaction liquid is diluted with ice water (200 ml) and extracted with chloroform (200 ml  $\times$  3). The chloroform phase is dried with magnesium sulfate, filtered and evaporated to dryness. The residue is blended with celite and subjected to column chromatography on silica gel (eluent: 1%  $\text{MeOH}-\text{CHCl}_3$ ) whereby 10-bromo-1,2,6,7-tetrahydrocamptothecin (MS:  $m/e$  430 [ $\text{M}^+$ ], 432 [ $\text{M}+2$ ]  $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_4\text{Br}=431$ ) is obtained. This compound is dissolved in dioxane (20 ml). To this solution is added DDQ (264 mg, 0.58 m-mol), and the mixture is boiled under reflux for 40 minutes. The reaction mixture is evaporated until dryness under reduced pressure and the residue is dissolved in chloroform (300 ml) and washed with water (200 ml  $\times$  2). The chloroform phase is dried with magnesium sulfate, filtered and evaporated until dryness under reduced pressure. The residue is blended with celite and purified by column chromatography on silica gel (eluent: 1% pyridine-chloroform) whereby 155 mg (yield: 36.3% from 1-acetyl-10-nitro-1,2,6,7-tetrahydrocamptothecin) of the title compound is obtained as white crystals.

This end product can also be prepared from 10-aminocamptothecin by diazotization followed by substitution reaction with cuprous bromide in the same manner as described above.

M.P. (with decomp.) 273–275°C (from  $\text{CHCl}_3$ ).

NMR (in  $\text{DMSO}-d_6$ )  $\delta$ : 0.89 (3H, t,  $J=7\text{Hz}$ ,  $-\text{CH}_2\text{CH}_3$ ), 1.87 (2H, q,  $J=7\text{Hz}$ ,  $-\text{CH}_2\text{CH}_3$ ), 5.28 (2H, s, C—5—H), 5.41 (2H, s, C—17—H), 6.48 (1H, s, C—20—OH), 7.34 (1H, s, C—14—H), 7.93 (1H, d, d,  $J=9\text{Hz}$ , 2Hz, C—11—H), 8.09 (1H, d,  $J=9\text{Hz}$ , C—12—H), 8.41 (1H, d,  $J=2\text{Hz}$ , C—9—H), 8.63 (1H, s, C—7—H).

$\text{IR}_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 3400, 1750, 1655, 1590, 1225, 1160.

MS:  $m/e$  426 [ $\text{M}^+$ ], 428 [ $\text{M}+2$ ]  $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_4\text{Br}=426$ .

#### Example 18

##### Preparation of 7-ethyl-5,10-dihydroxycamptothecin:

7-Ethyl-10-hydroxycamptothecin (50 mg, 0.128 m-mol) is dissolved in dimethylformamide (20 ml). To this solution are added anhydrous potassium carbonate (150 mg) and iodine (40 mg, 0.157 m-mol), and the mixture is stirred for 5 hours at room temperature. Any insoluble matter is then removed by filtration and the filtrate is evaporated until dryness. The residue is purified by way of column chromatography on silica gel whereby 35 mg (67.0%) of the title compound is obtained.

$^1\text{H}$ -NMR (in  $\text{DMSO}-d_6$ )  $\delta$  ppm: 0.90 (3H, t,  $J=7.5\text{Hz}$ ), 1.30 (3H, t,  $J=7.5\text{Hz}$ ), 1.90 (2H, q,  $J=7.5\text{Hz}$ ), 3.30 (2H, q, 7.5Hz), 5.40 (2H, s), 6.50 (1H, s), 7.0–8.0 (6H, m), 10.30 (1H, s).

MS:  $m/e$  408 [ $\text{M}^+$ ], for  $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_6=408$ .

## Example 19

Preparation of 7-ethyl-10-hydroxy-5-methoxycamptothecin:

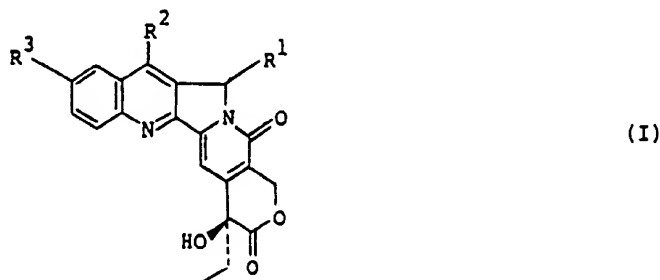
7-Ethyl-5,10-dihydroxycamptothecin (20 mg, 0.049 m-mol) is suspended in methanol (30 ml). To this suspension is added conc. sulfuric acid (0.5 ml), and the mixture is stirred for 48 hours. The solvent is then distilled off under reduced pressure and the residue is dissolved in chloroform and washed with water. The chloroform phase is dried with anhydrous magnesium sulfate and then evaporated until dryness under reduced pressure. The residue is purified by way of column chromatography on silica gel whereby the title compound (18 mg, 87.0%) is obtained.

$^1\text{H-NMR}$  (in  $\text{CDCl}_3$ ) ppm: 1.00 (3H, t,  $J=7.5\text{Hz}$ ), 1.25 (3H, t,  $J=7.5\text{Hz}$ ), 1.95 (2H, q,  $J=7.5\text{Hz}$ ), 3.40 (2H, q,  $J=7.5\text{Hz}$ ), 4.00, (3H, s), 5.44 (2H, ABq), 6.80–8.10 (5H, m).

MS:  $m/e$  422 [ $M^+$ ], for  $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_6=422$ .

## Claims

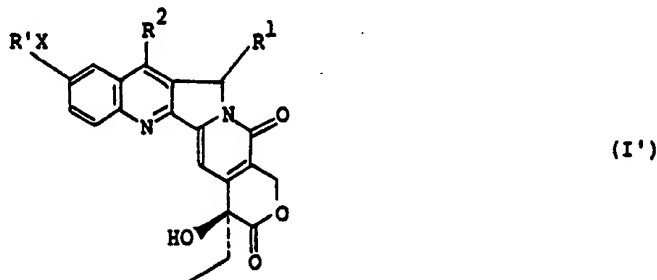
1. A camptothecin derivative of the formula:



wherein  $R^1$  is a hydrogen atom, a  $\text{C}_1\text{--C}_{30}$  alkyl group, a  $\text{C}_5\text{--C}_8$  cycloalkyl group, a hydroxyl group, a  $\text{C}_1\text{--C}_{30}$  alkoxy group or a  $\text{C}_1\text{--C}_{17}$  acyloxy group,  $R^2$  is a  $\text{C}_1\text{--C}_{30}$  alkyl group, a  $\text{C}_5\text{--C}_8$  cycloalkyl group, a phenylalkyl group, a naphthylalkyl group, a hydroxymethyl group, a carboxymethyl group or a  $\text{C}_1\text{--C}_{17}$  acyloxymethyl group, and  $R^3$  is the grouping  $\text{--XR'}$  (in which  $R'$  is a hydrogen atom, a  $\text{C}_1\text{--C}_{30}$  alkyl group, a  $\text{C}_5\text{--C}_8$  cycloalkyl group, or a  $\text{C}_1\text{--C}_{17}$  acyl group and  $X$  is an oxygen atom or a sulfur atom), and wherein the alkyl, alkoxy, acyl and acyloxy groups may be substituted with one or more halo, nitro, amino, carboalkoxy, alkylamino, dialkylamino or alkoxy groups as defined above.

2. A camptothecin derivative which is a 10-hydroxy-7- $\text{C}_{1\text{--}30}$ -alkylcamptothecin, 10-hydroxy-7-phenylalkylcamptothecin, 10-hydroxy-7-naphthylalkylcamptothecin, 10-hydroxy-7-hydroxymethylcamptothecin, 10-hydroxy-7- $\text{C}_{1\text{--}17}$ -acyloxymethylcamptothecin, 10-hydroxy-7-carboxymethylcamptothecin, 10- $\text{C}_{1\text{--}30}$ -alkoxy-7- $\text{C}_{1\text{--}30}$ -alkylcamptothecin, 10- $\text{C}_{1\text{--}30}$ -alkoxy-7-phenylalkylcamptothecin, 10- $\text{C}_{1\text{--}30}$ -alkoxy-7-naphthylalkylcamptothecin, 10- $\text{C}_{1\text{--}30}$ -alkoxy-7-hydroxymethylcamptothecin, 10- $\text{C}_{1\text{--}30}$ -alkoxy-7- $\text{C}_{1\text{--}17}$ -acyloxymethylcamptothecin, 10- $\text{C}_{1\text{--}17}$ -acyloxy-7- $\text{C}_{1\text{--}10}$ -alkylcamptothecin, 10- $\text{C}_{1\text{--}17}$ -acyloxy-7-phenylalkyl- or 7-naphthylalkylcamptothecin, 10- $\text{C}_{1\text{--}17}$ -acyloxy-7-hydroxymethylcamptothecin, 10- $\text{C}_{1\text{--}17}$ -acyloxy-7- $\text{C}_{1\text{--}17}$ -acyloxymethylcamptothecin, the alkyl, alkoxy, acyl and acyloxy groups being optionally substituted as defined in claim 1.

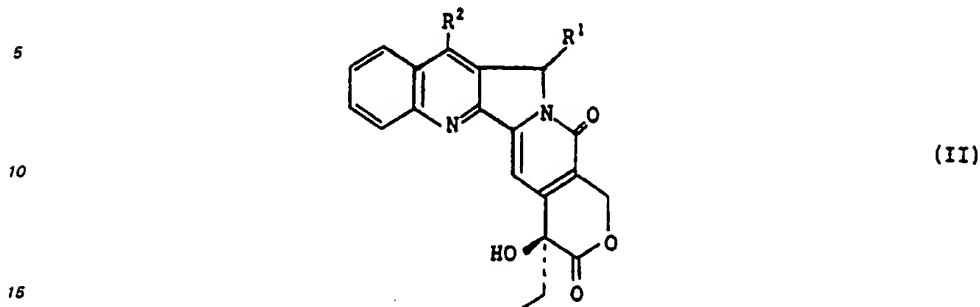
3. A process for the preparation of 10-substituted camptothecin derivatives of the general formula:



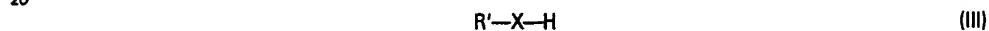
wherein  $R^1$  is a hydrogen atom, a  $\text{C}_1\text{--C}_{30}$  alkyl group, a  $\text{C}_5\text{--C}_8$  cycloalkyl group, a hydroxyl group, a  $\text{C}_1\text{--C}_{30}$  alkoxy group or a  $\text{C}_1\text{--C}_{17}$  acyloxy group,  $R^2$  is a hydrogen atom, a  $\text{C}_1\text{--C}_{30}$  alkyl group, a  $\text{C}_5\text{--C}_8$  cycloalkyl group, a phenylalkyl group, a naphthylalkyl group, a hydroxymethyl group, a carboxymethyl group or a  $\text{C}_1\text{--C}_{17}$  acyloxymethyl group,  $R'$  is a hydrogen atom, a  $\text{C}_1\text{--C}_{30}$  alkyl group, a  $\text{C}_5\text{--C}_8$  cycloalkyl group, or a  $\text{C}_1\text{--C}_{17}$  acyl group, and  $X$  is an oxygen atom or a sulfur atom, the alkyl, alkoxy, acyl and acyloxy

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groups being optionally substituted as defined in Claim 1, characterized by treating camptothecin or a 5- and/or 7-substituted camptothecin derivative of the general formula:



wherein R¹ and R² have the same meanings as given above, with a peroxidant in a liquid vehicle and then reacting the resultant camptothecin-1-oxide or 5- and/or 7-substituted camptothecin-1-oxide derivative with an active hydrogen-containing reagent of the general formula:

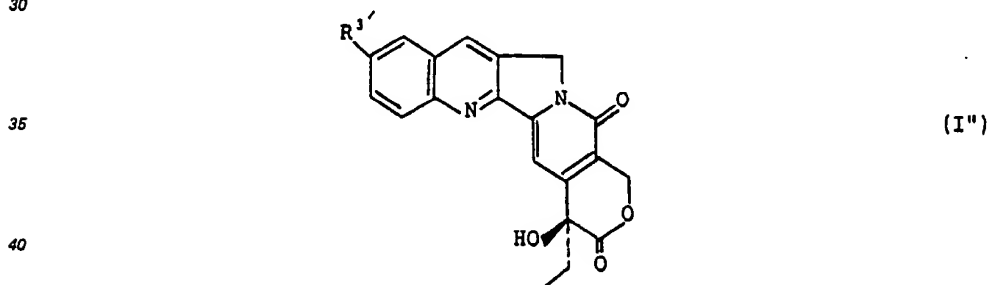


wherein R¹ and X have the same meanings as given above, in the presence of an acid under irradiation with ultraviolet rays.

25 4. A process according to claim 3, wherein the peroxidant is hydrogen peroxide, an inorganic or organic peracid or a salt thereof.

5. A process according to claim 3 or claim 4, wherein the liquid vehicle is glacial acetic acid or an aqueous solution thereof, a liquid hydrocarbon or a liquid chlorinated hydrocarbon, or an ether.

6. A process for the preparation of 10-substituted camptothecin derivatives of the general formula:



wherein R³' is nitro group, an amino group, a C₁-C₈ alkylamino group, a C₁-C₁₇ acylamino group, a hydroxyl group or a halogen atom, the alkyl and acyl groups being optionally substituted as defined in claim 1, characterized by catalytically hydrogenated camptothecin in a solvent under atmospheric pressure in the presence of a noble metal catalyst, treating the resultant 1,2,6,7-tetrahydrocamptothecin with an acylating agent to introduce an acyl group into the 1-position, treating the thus-obtained 1-acyl-1,2,6,7-tetrahydrocamptothecin with a mixture of nitric acid and sulfuric acid, eliminating the 1-acyl group in the resultant 1-acyl-10-nitro-1,2,6,7-tetrahydrocamptothecin by hydrolysis under acidic or alkaline conditions, and then either (a) treating the resultant 10-nitro-1,2,6,7-tetrahydrocamptothecin with an oxidizing agent to cause dehydrogenation of the saturated ring and optionally reducing the resultant 10-nitro-camptothecin to convert the nitro group into an amino group, or (b) converting the nitro group of the resultant 10-nitro-1,2,6,7-tetrahydrocamptothecin into an amino group by reduction and treating the resulting amino compound with an oxidizing agent as in (a), or (c) starting with either 10-amino-1,2,6,7-tetrahydrocamptothecin produced by the initial reduction of (b) or with 10-aminocamptothecin resulting from either (a) or (b) modifying the amino group by N-alkylation or N-acylation or by diazotization followed by hydrolysis or reaction with a cuprous halide to convert the amino group into a hydroxyl group or a halogen atom, and, if necessary, treating the resulting 10-modified 1,2,6,7-tetrahydrocamptothecin derivative with an oxidizing agent to cause dehydrogenation of the saturated ring.

7. A process according to claim 6, wherein the noble metal catalyst is platinum black, platinum oxide, palladium black or palladium oxide, if desired, carried on carbon black.

8. A process according to claim 6 or claim 7, wherein the oxidizing agent is dichlorodicyanobenzoquinone, air or nitric acid.

9. A process according to any one of claims 6 to 8, wherein 10-nitro-1,2,6,7-tetrahydrocamptothecin is reduced prior to oxidation to cause dehydrogenation of the saturated ring.

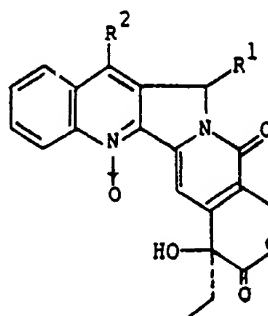


10. A pharmaceutical or veterinary formulation comprising a compound according to claim 1 or claim 2 formulated for pharmaceutical or veterinary use, respectively.

11. A compound as defined in claim 1 or claim 2 for use in producing an anti-tumor effect in man or any other animal.

12. A process for preparing a pharmaceutical or veterinary formulation which comprises (1) preparing a 10-substituted camptothecin derivative of formula (I') or (I'') by a process as defined in any one of claims 3 to 5 or 6 to 9, respectively and (2) formulating the 10-substituted camptothecin for pharmaceutical or veterinary use, respectively.

13. A 5- and/or 7-substituted camptothecin-1-oxide derivative of the formula:



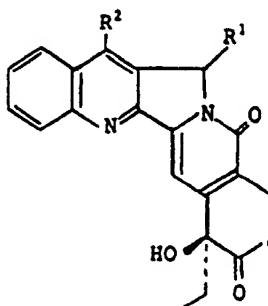
(IV)

wherein R<sup>1</sup> and R<sup>2</sup> are as defined in claim 3, with the proviso that R<sup>1</sup> and R<sup>2</sup> are not both hydrogen atoms.

14. 5-(C<sub>1</sub>—C<sub>30</sub>)Alkylcamptothecin-1-oxide, 5-(C<sub>1</sub>—C<sub>30</sub>)alkoxycamptothecin-1-oxide, 7-(C<sub>1</sub>—C<sub>30</sub>)alkylcamptothecin-1-oxide, 7-phenylalkyl- or 7-naphthylalkyl-camptothecin-1-oxide, 7-(C<sub>1</sub>—C<sub>17</sub>)acyloxymethylcamptothecin-1-oxide or 7-hydroxymethylcamptothecin-1-oxide.

15. 5-(C<sub>1</sub>—C<sub>17</sub>)Acyloxycamptothecin-1-oxide, 5-hydroxycamptothecin-1-oxide or 7-carboxymethylcamptothecin-1-oxide.

16. A process for the preparation of 5- and/or 7-substituted camptothecin derivatives as defined in claim 13, characterized by treating a 5- and/or 7-substituted camptothecin derivative of the general formula:



(II)

wherein R<sup>1</sup> and R<sup>2</sup> are as defined in claim 13, with a peroxidant in a liquid vehicle.

17. A process according to claim 16, wherein the peroxidant is hydrogen peroxide, a persulfate or m-chloroperbenzoic acid.

18. A process according to claim 16 or claim 17, wherein the liquid vehicle is acetic acid.

19. A process according to any one of claims 16 to 18, wherein the 5- and/or 7-substituted camptothecin derivative is treated with hydrogen peroxide at a temperature in the range from 60°C to 80°C.

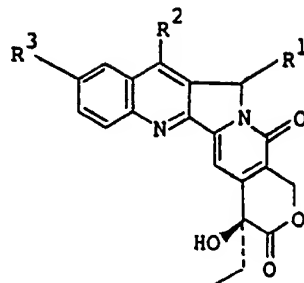
## Patentansprüche

## 1. Camptothecin-Derivate der Formel

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(I)

20 worin  $R^1$  ein Wasserstoffatom, eine  $C_1$ – $C_{30}$ -Alkylgruppe, eine  $C_5$ – $C_8$ -Cycloalkylgruppe, eine Hydroxylgruppe, eine  $C_1$ – $C_{30}$ -Alkoxygruppe oder eine  $C_1$ – $C_{17}$ -Acyloxygruppe;  $R^2$  eine  $C_1$ – $C_{30}$ -Alkylgruppe, eine  $C_5$ – $C_8$ -Cycloalkylgruppe, eine Phenylalkylgruppe, eine Naphthylalkylgruppe, eine Hydroxymethylgruppe, eine Carboxymethylgruppe oder eine  $C_1$ – $C_{17}$ -Acyloxymethylgruppe und  $R^3$  die Gruppe  $-XR'$ , worin  $R'$  ein Wasserstoffatom, eine  $C_1$ – $C_{30}$ -Alkylgruppe, eine  $C_5$ – $C_8$ -Cycloalkylgruppe oder  
 25 eine  $C_1$ – $C_{17}$ -Acylgruppe und X ein Sauerstoffatom oder ein Schwefelatom darstellen, bedeuten und worin die Alkyl-, Alkoxy-, Acyl- und Acyloxygruppen durch ein oder mehrere Halogenatome, Nitro-, Amino-, Carboalkoxy-, Alkylamino-, Dialkylamino- oder Alkoxygruppen (wie vorstehend definiert) substituiert sein können.

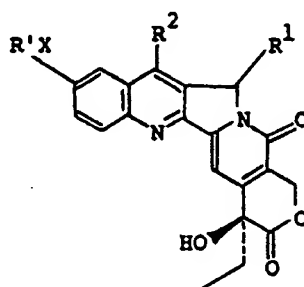
2. Camptothecin-Derivat, nämlich 10-Hydroxy-7- $C_{1-30}$ -alkylcamptothecin, 10-Hydroxy-7-phenylalkyl-  
 30 camptothecin, 10-Hydroxy-7-naphthylalkylcamptothecin, 10-Hydroxy-7-hydroxymethylcamptothecin, 10-Hydroxy-7- $C_{1-17}$ -acyloxymethylcamptothecin, 10-Hydroxy-7-carboxymethylcamptothecin, 10- $C_{1-30}$ -Alkoxy-7- $C_{1-30}$ -alkylcamptothecin, 10- $C_{1-30}$ -Alkoxy-7-phenylalkylcamptothecin, 10- $C_{1-30}$ -Alkoxy-7-naphthylalkylcamptothecin, 10- $C_{1-30}$ -Alkoxy-7-hydroxymethylcamptothecin, 10- $C_{1-30}$ -Alkoxy-7- $C_{1-17}$ -  
 35 acyloxymethylcamptothecin, 10- $C_{1-17}$ -Acyloxy-7- $C_{1-30}$ -alkylcamptothecin, 10- $C_{1-17}$ -Acyloxy-7-phenylalkyl- oder 7-Naphthylalkylcamptothecin, 10- $C_{1-17}$ -Acyloxy-7-hydroxymethylcamptothecin, 10- $C_{1-17}$ -Acyloxy-7- $C_{1-17}$ -acyloxymethylcamptothecin, worin die Alkyl-, Alkoxy-, Acyl- und Acyloxygruppen gegebenenfalls, wie in Anspruch 1 definiert, substituiert sind.

3. Verfahren zur Herstellung von 10-substituierten Camptothecin-Derivaten der allgemeinen Formel

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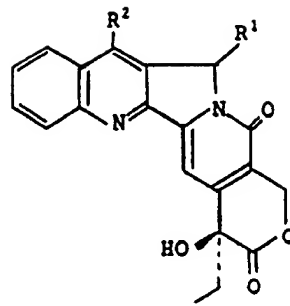


(I')

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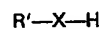
50 worin  $R^1$  ein Wasserstoffatom, eine  $C_1$ – $C_{30}$ -Alkylgruppe, eine  $C_5$ – $C_8$ -Cycloalkylgruppe, eine Hydroxylgruppe, eine  $C_1$ – $C_{30}$ -Alkoxygruppe oder eine  $C_1$  bis  $C_{17}$ -Acyloxygruppe;  $R^2$  ein Wasserstoffatom, eine  $C_1$  bis  $C_{30}$ -Alkylgruppe, eine  $C_5$ – $C_8$ -Cycloalkylgruppe, eine Phenylalkylgruppe, eine Naphthyl-  
 60 alkylgruppe, eine Hydroxymethylgruppe, eine Carboxymethylgruppe oder eine  $C_1$ – $C_{17}$ -Acyloxymethylgruppe;  $R'$  ein Wasserstoffatom, eine  $C_1$ – $C_{30}$ -Alkylgruppe, eine  $C_5$ – $C_8$ -Cycloalkylgruppe oder eine  $C_1$ – $C_{17}$ -Acylgruppe; und X ein Sauerstoffatom oder ein Schwefelatom darstellen, wobei die Alkyl-, Alkoxy-, Acyl- und Acyloxygruppen gegebenenfalls, wie in Anspruch 1 definiert, substituiert sind, dadurch gekennzeichnet, daß man Camptothecin oder ein 5- und/oder 7-substituiertes Camptothecin-Derivat der  
 65 allgemeinen Formel

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(II)

15 worin  $R^1$  und  $R^2$  die vorstehend angegebenen Bedeutungen haben, mit einem Peroxidationsmittel in einem flüssigen Träger oxidiert und das erhaltene Camptothecin-1-Oxid oder 5- und/oder 7-substituierte Camptothecin-1-Oxid-Derivat mit einem aktiven Wasserstoff enthaltenden Reagens der allgemeinen Formel



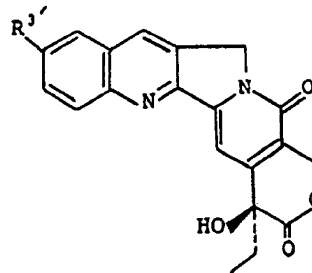
(III)

20 worin  $R'$  und  $X$  die vorstehend angegebenen Bedeutungen haben, in Gegenwart einer Säure unter Bestrahlung mit Ultraviolett-Strahlen umsetzt.

4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß man als Peroxidationsmittel Wasserstoffperoxid, eine anorganische oder organische Persäure oder ein Salz davon verwendet.

25 5. Verfahren nach Anspruch 3 oder 4, dadurch gekennzeichnet, daß der flüssige Träger Eisessig oder eine wäßrige Lösung davon, einen flüssigen Kohlenwasserstoff, einen flüssigen chlorierten Kohlenwasserstoff oder einen Äther darstellt.

6. Verfahren zur Herstellung von 10-substituierten Camptothecin-Derivaten der allgemeinen Formel

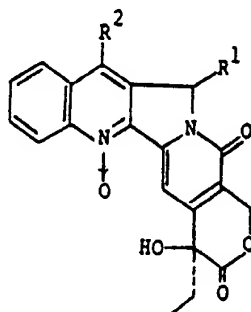


(I'')

35 worin  $R^{3'}$  eine Stickstoffgruppe, eine Aminogruppe, eine  $C_1-C_8$ -Alkylaminogruppe, eine  $C_1-C_{17}$ -Acylaminogruppe, eine Hydroxylgruppe oder ein Halogenatom darstellt, wobei die Alkyl- und Acylgruppen gegebenenfalls, wie in Anspruch 1 definiert, substituiert sind, darstellt, dadurch gekennzeichnet, daß man Camptothecin in einem Lösungsmittel unter Atmosphärendruck in Gegenwart eines Edelmetallkatalysators katalytisch hydriert, das erhaltene 1,2,6,7-Tetrahydrocamptothecin mit einem Acylierungsmittel behandelt, um eine Acylgruppe in die 1-Stellung einzuführen, das so erhaltene 1-Acyl-1,2,6,7-Tetrahydrocamptothecin mit einem Gemisch aus Salpetersäure und Schwefelsäure behandelt, die 1-Acylgruppe in dem erhaltenen 1-Acyl-10-nitro-1,2,6,7-tetrahydrocamptothecin durch Hydrolyse unter sauren oder alkalischen Bedingungen eliminiert und anschließend entweder (a) das erhaltene 10-Nitro-1,2,6,7-tetrahydrocamptothecin mit einem Oxidationsmittel zwecks Dehydrierung des gesättigten Ringes behandelt und gegebenenfalls das erhaltene 10-Nitro-Camptothecin reduziert, um die Nitrogruppe in eine Aminogruppe umzuwandeln, oder (b) die Nitrogruppe des erhaltenen 10-Nitro-1,2,6,7-tetrahydrocamptothecins durch Reduktion in eine Aminogruppe umwandelt und die erhaltene Aminogruppe mit einem Oxidationsmittel wie in (a) behandelt; oder (c) ausgehend von 10-Amino-1,2,6,7-Tetrahydrocamptothecin aus der anfänglichen Reduktion von (b) oder von 10-Aminocamptothecin, aus (a) oder (b), die Aminogruppe durch N-Alkylierung oder N-Acylierung oder durch Diazotierung modifiziert und anschließend eine Hydrolyse oder eine Reaktion mit einem Kupfer(I)-Halogenid durchführt, um die Aminogruppe in eine Hydroxylgruppe bzw. in ein Halogenatom umzuwandeln und, falls erforderlich, das erhaltene 10-modifizierte 1,2,6,7-Tetrahydrocamptothecin-Derivat mit einem Oxidationsmittel behandelt, um eine Dehydrierung des gesättigten Ringes zu bewirken.

7. Verfahren nach Anspruch 6, worin der Edelmetallkatalysator Platinschwarz, Platinoxid, Palladiumschwarz oder Palladiumoxid, gegebenenfalls auf Ruß als Träger, darstellt.

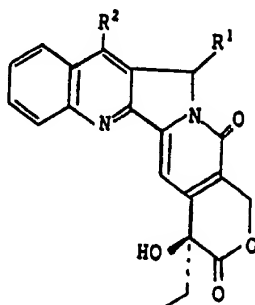
8. Verfahren nach Anspruch 6 oder 7, worin das Oxidationsmittel Dichlordicyanobenzochinon, Luft oder Salpetersäure darstellt.
9. Verfahren nach einem der Ansprüche 6 bis 8, worin das 10-Nitro-1,2,6,7-Tetrahydrocamptothecin vor der Oxidation zwecks Dehydrierung des gesättigten Ringes reduziert wird.
10. Pharmazeutische oder veterinärmedizinische Zubereitung, enthaltend eine Verbindung nach Anspruch 1 oder 2, die für den pharmazeutischen oder veterinärmedizinischen Gebrauch formuliert ist.
11. Verbindung nach Anspruch 1 oder 2, zur Erzeugung einer Anti-Tumor-Wirkung beim Menschen oder einem anderen Lebewesen.
12. Verfahren zur Herstellung einer pharmazeutischen oder veterinärmedizinischen Zubereitung, wobei (1) ein 10-substituiertes Camptothecin-Derivat gemäß Formel (I'), oder (I'') nach einem Verfahren nach einem der Ansprüche 3 bis 5 bzw. 6 bis 9 hergestellt wird und (2) das 10-substituierte Camptothecin für den pharmazeutischen bzw. veterinärmedizinischen Gebrauch zubereitet wird.
13. 5- und/oder 7-substituiertes Camptothecin-1-oxid-Derivat der Formel



(IV)

worin R<sup>1</sup> und R<sup>2</sup> wie in Anspruch 3 definiert sind, mit der Maßgabe, daß R<sup>1</sup> und R<sup>2</sup> nicht beide Wasserstoffatome darstellen.

14. 5-(C<sub>1</sub>—C<sub>30</sub>)Alkylcamptothecin-1-oxid, 5-(C<sub>1</sub>—C<sub>30</sub>)Alkylcamptothecin-1-oxid, 7-(C<sub>1</sub>—C<sub>30</sub>)-alkylcamptothecin-1-oxid, 7-Phenylalkyl- oder 7-Naphthylalkyl-camptothecin-1-oxid, 7-(C<sub>1</sub>—C<sub>17</sub>)Acyloxy-methylcamptothecin-1-oxid oder 7-Hydroxymethylcamptothecin-1-oxid.
15. 5-(C<sub>1</sub>—C<sub>17</sub>)Acyloxy-camptothecin-1-oxid, 5-Hydroxycamptothecin-1-oxid oder 7-Carboxymethyl-camptothecin-1-oxid.
16. Verfahren zur Herstellung von 5- und/oder 7-substituierten Camptothecin-Derivaten nach Anspruch 13, dadurch gekennzeichnet, daß man ein 5- und/oder 7-substituiertes Camptothecin-Derivat der



(II)

worin R<sup>1</sup> und R<sup>2</sup> wie in Anspruch 13 definiert sind, mit einem Peroxidationsmittel in einem flüssigen Träger umgesetzt.

17. Verfahren nach Anspruch 16, worin das Peroxidationsmittel Wasserstoffperoxid, ein Persulfat oder m-Chlorperbenzoesäure darstellt.
18. Verfahren nach Anspruch 16 oder 17, worin der flüssige Träger Essigsäure darstellt.
19. Verfahren nach einem der Ansprüche 16 bis 18, worin das 5- und/oder 7-substituierte Camptothecin-Derivat mit Wasserstoffperoxid bei einer Temperatur im Bereich von 60 bis 80°C behandelt wird.

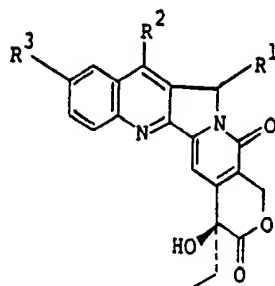
## Revendications

## 1. Dérivé de camptothécine de formule

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(I)

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où R<sup>1</sup> est un atome d'hydrogène, un radical C<sub>1</sub>-C<sub>30</sub>-alcoyle, un radical C<sub>5</sub>-C<sub>8</sub>-cycloalcoyle, un radical hydroxyle, un radical C<sub>1</sub>-C<sub>30</sub>-alcoxy ou un radical C<sub>1</sub>-C<sub>17</sub>-acyloxy, R<sup>2</sup> est un radical C<sub>1</sub>-C<sub>30</sub>-alcoyle, un radical C<sub>5</sub>-C<sub>8</sub>-cycloalcoyle, un radical phénylcoyle, un radical naphthylcoyle, un radical hydroxyméthyle, un radical carboxyméthyle ou un radical C<sub>1</sub>-C<sub>17</sub>-acyloxyméthyle et R<sup>3</sup> est le groupement —XR' (où R' est un atome d'hydrogène, un radical C<sub>1</sub>-C<sub>30</sub>-alcoyle, un radical C<sub>5</sub>-C<sub>8</sub>-cycloalcoyle ou un radical C<sub>1</sub>-C<sub>17</sub>-acyle et X est un atome d'oxygène ou un atome de soufre) et dont les radicaux alcoyle, alcoxy, acyle et acyloxy peuvent être substitués par un ou plusieurs radicaux halo, nitro, amino, carboalcoyle, alcoylamino, dialcoylamino ou alcoxy tels que définis ci-dessus.

2. Dérivé de camptothécine, qui est une 10-hydroxy-7-C<sub>1</sub>-C<sub>30</sub>-alcoylcamptothécine, une 10-hydroxy-7-phénylcoylcamptothécine, une 10-hydroxy-7-naphthylcoylcamptothécine, la 10-hydroxy-7-hydroxyméthylcamptothécine, une 10-hydroxy-7-C<sub>1</sub>-C<sub>17</sub>-acyloxyméthylcamptothécine, la 10-hydroxy-7-carboxyméthylcamptothécine, une 10-C<sub>1</sub>-C<sub>30</sub>-alcoxy-7-C<sub>1</sub>-C<sub>30</sub>-alcoylcamptothécine, une 10-C<sub>1</sub>-C<sub>30</sub>-alcoxy-7-phénylcoylcamptothécine, une 10-C<sub>1</sub>-C<sub>30</sub>-alcoxy-7-naphthylcoylcamptothécine, une 10-C<sub>1</sub>-C<sub>30</sub>-alcoxy-7-hydroxyméthylcamptothécine, une 10-C<sub>1</sub>-C<sub>30</sub>-alcoxy-7-C<sub>1</sub>-C<sub>17</sub>-acyloxyméthylcamptothécine, une 10-C<sub>1</sub>-C<sub>17</sub>-acyloxy-7-C<sub>1</sub>-C<sub>10</sub>-alcoylcamptothécine, une 10-C<sub>1</sub>-C<sub>17</sub>-acyloxy-7-phénylcoyl- ou 7-naphthylcoylcamptothécine, une 10-C<sub>1</sub>-C<sub>17</sub>-acyloxy-7-hydroxyméthylcamptothécine, 10-C<sub>1</sub>-C<sub>17</sub>-acyloxy-7-C<sub>1</sub>-C<sub>17</sub>-acyloxyméthylcamptothécine, les radicaux alcoyle, alcoxy, acyle et acyloxy étant éventuellement substitués comme défini dans la revendication 1.

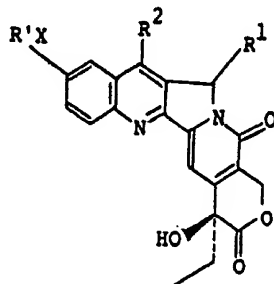
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3. Procédé de préparation de dérivés de camptothécine-10-substitués de formule générale:

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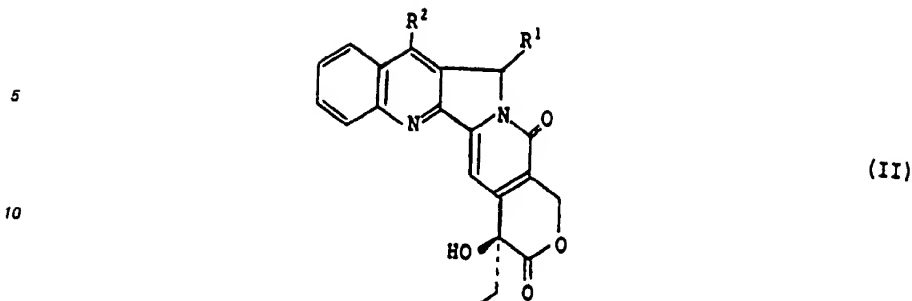
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(I')

où R<sup>1</sup> est un atome d'hydrogène, un radical C<sub>1</sub>-C<sub>30</sub>-alcoyle, un radical C<sub>5</sub>-C<sub>8</sub>-cycloalcoyle, un radical hydroxyle, un radical C<sub>1</sub>-C<sub>30</sub>-alcoxy ou un radical C<sub>1</sub>-C<sub>17</sub>-acyloxy, R<sup>2</sup> est un atome d'hydrogène, un radical C<sub>1</sub>-C<sub>30</sub>-alcoyle, un radical C<sub>5</sub>-C<sub>8</sub>-cycloalcoyle, un radical phénylcoyle, un radical naphthylcoyle, un radical hydroxyméthyle, un radical carboxyméthyle ou un radical C<sub>1</sub>-C<sub>17</sub>-acyloxyméthyle, R' est un atome d'hydrogène, un radical C<sub>1</sub>-C<sub>30</sub>-alcoyle, un radical C<sub>5</sub>-C<sub>8</sub>-cycloalcoyle ou un radical C<sub>1</sub>-C<sub>17</sub>-acyle, et X est un atome d'oxygène ou de soufre, les radicaux alcoyle, alcoxy, acyle et acyloxy étant éventuellement substitués comme défini dans la revendication 1, caractérisé en ce qu'on traite la camptothécine ou un dérivé de camptothécine 5- et/ou 7-substitué de la formule générale:



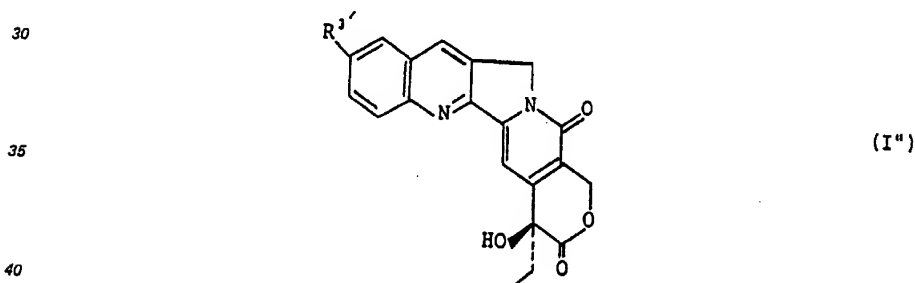
15 où R<sup>1</sup> et R<sup>2</sup> ont les mêmes significations que celles indiquées ci-dessus, avec un peroxydant dans un véhicule liquide, puis on fait réagir le camptothécine-1-oxyde ou dérivé de camptothécine-1-oxyde 5- et/ou 7-substitué résultant avec un réactant contenant de l'hydrogène actif de formule générale:



(III)

où R' et X ont les mêmes significations que celles indiquées ci-dessus, en présence d'un acide sous irradiation par le rayonnement UV.

4. Procédé suivant la revendication 3, dans lequel le peroxydant est le peroxyde d'hydrogène, un peracide inorganique ou organique ou un sel de celui-ci.
5. Procédé suivant la revendication 3 ou 4, dans lequel le véhicule liquide est l'acide acétique glacial ou une solution aqueuse de celui-ci, un hydrocarbure liquide, un hydrocarbure liquide chloré ou un éther.
6. Procédé de préparation de dérivés de camptothécine 10-substitués de formule générale:



où R<sup>3'</sup> est un radical nitro, un radical amino, un radical C<sub>1</sub>-C<sub>8</sub>-alcoylamino, un radical C<sub>1</sub>-C<sub>17</sub>-acylamino, un radical hydroxyle ou un atome d'halogène, les radicaux alcoyle et acyle étant éventuellement substitués comme défini dans la revendication 1, caractérisé par l'hydrogénation catalytique de la camptothécine dans un solvant sous la pression atmosphérique en présence d'un métal noble catalytique, le traitement de la 1,2,6,7-tétrahydrocamptothécine résultante au moyen d'un agent d'acylation pour introduire un radical acyle à la position 1, le traitement de la 1-acyl-1,2,6,7-tétrahydrocamptothécine ainsi obtenue au moyen d'un mélange d'acide nitrique et d'acide sulfurique, l'élimination du radical 1-acyle de la 1-acyl-10-nitro-1,2,6,7-tétrahydrocamptothécine résultante par hydrolyse dans des conditions acides ou alcalines et

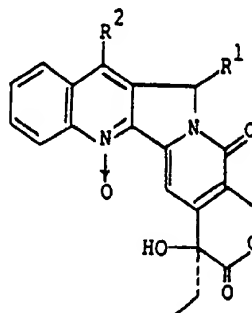
50 ensuite soit (a) le traitement de la 10-nitro-1,2,6,7-tétrahydrocamptothécine résultante au moyen d'un agent oxydant pour provoquer le déshydrogénation du cycle saturé, et éventuellement la réduction de la 10-nitrocamptothécine résultante pour la conversion du radical nitro en un radical amino, soit (b) la conversion du radical nitro de 10-nitro-1,2,6,7-tétrahydrocamptothécine résultante en un radical amino par réduction et le traitement du composé aminé résultant au moyen d'un agent oxydant comme en (a), soit (c) à partir de la 10-amino-1,2,6,7-tétrahydrocamptothécine produite par la réduction initiale en (b) ou à partir de la 10-aminocamptothécine résultant de (a) ou de (b), la modification du radical amino par N-alcoylation ou N-acylation ou par diazotation suivie d'hydrolyse ou de réaction avec un halogénure cuivreux pour convertir le radical amino en un radical hydroxyle ou un atome d'halogène et, si nécessaire, le traitement du dérivé de 1,2,6,7-tétrahydrocamptothécine 10-modifié résultant au moyen d'un agent oxydant pour

60 provoquer la déshydrogénation du cycle saturé.

7. Procédé suivant la revendication 6, dans lequel le métal noble catalytique est le noir de platine, l'oxyde de platine, le noir de palladium ou l'oxyde de palladium, si la chose est souhaitée, déposés sur du noir de carbone.

8. Procédé suivant la revendication 6 ou 7, dans lequel l'agent oxydant est la dichlorodicyanobenz quinone, l'air ou l'acide nitrique.

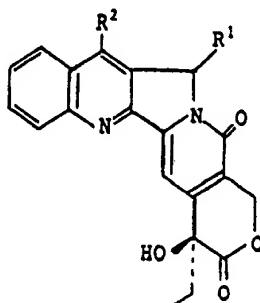
9. Procédé suivant l'une quelconque des revendications 6 à 8, dans lequel la 10-nitro-1,2,6,7-tétrahydrocamptothécine est réduite avant l'oxydation provoquant la déshydrogénation du cycle saturé.
10. Composition pharmaceutique ou vétérinaire comprenant un composé suivant la revendication 1 ou 2 mis en composition à usage pharmaceutique ou vétérinaire, respectivement.
11. Composé tel que défini dans la revendication 1 ou 2 à utiliser pour exercer un effet antitumoral chez l'homme ou un autre animal quelconque.
12. Procédé de préparation d'une composition pharmaceutique ou vétérinaire que comprend (1) la préparation d'un dérivé de camptothécine 10-substitué de formule (I') ou (I'') par un procédé tel que défini dans l'une quelconque des revendications 3 à 5 ou 6 à 9, respectivement, et (2) la mise en composition de la camptothécine 10-substituée à usage pharmaceutique ou vétérinaire, respectivement.
13. Dérivé de camptothécine-1-oxyde 5- et/ou 7-substitué de formule:



(IV)

où R<sup>1</sup> et R<sup>2</sup> sont tels que définis dans la revendication 3, avec la restriction que R<sup>1</sup> et R<sup>2</sup> ne sont pas tous deux des atomes d'hydrogène.

14. 5-(C<sub>1</sub>—C<sub>30</sub>)Alcoylcamptothécine-1-oxyde, 5-(C<sub>1</sub>—C<sub>30</sub>)alcoycamptothécine-1-oxyde, 7-(C<sub>1</sub>—C<sub>30</sub>)alcoylcamptothécine-1-oxyde, 7-phénylcoyl- ou 7-naphtylalcoylcamptothécine-1-oxyde, 7-(C<sub>1</sub>—C<sub>17</sub>)acyloxyméthylcamptothécine-1-oxyde ou 7-hydroxyméthylcamptothécine-1-oxyde.
15. 5-(C<sub>1</sub>—C<sub>17</sub>)Acyloxycamptothécine-1-oxyde, 5-hydroxycamptothécine-1-oxyde ou 7-carboxyméthylcamptothécine-1-oxyde.
16. Procédé de préparation de dérivés de camptothécine 5- et/ou 7-substitués tels que définis dans la revendication 13, caractérisé en ce qu'on traite un dérivé de camptothécine 5- et/ou 7-substitué de formule générale;



(II)

où R<sup>1</sup> et R<sup>2</sup> sont tels que définis dans la revendication 13, au moyen d'un peroxydant dans un véhicule liquide.

17. Procédé suivant la revendication 16, dans lequel le peroxydant est le peroxyde d'hydrogène, un persulfate ou l'acide m-chloroperbenzoïque.
18. Procédé suivant la revendication 16 ou 17, caractérisé en ce que le véhicule liquide est l'acide acétique.
19. Procédé suivant l'une quelconque des revendications 16 à 18, dans lequel le dérivé de camptothécine 5- et/ou 7-substitué est traité au moyen de peroxyde d'hydrogène à une température de l'intervalle de 60°C à 80°C.